The New England
Journal of Medicine

Copyright, 1949, by the Massachusetts Medical Society

Volume 241 DECEMBER 15, 1949 Number 24

THE VALUE OF THE THORACOABDOMINAL INCISION IN THE REMOVAL OF KIDNEY TUMORS*

RICHARD CHUTE, M.D.,† LAMAR SOUTTER, M.D.,‡ AND WALTER S. KERR, JR., M.D.§

BOSTON

ALTHOUGH the kidneys are situated below the diaphragm, they lie to a large extent within the thorax, sheltered by the lower ribs. Chiefly because the unyielding bony thoracic cage frequently bars the way to a free and satisfactory surgical exposure of the upper portion of the kidneys when they are enlarged, the lumbar extraperitoneal incision commonly used for renal surgery, with or without removal of the twelfth rib, and also the transperitoneal approach often leave a great deal to be desired in the way of exposure when one is dealing with large tumors of the kidney. While searching for an incision that would give better access to and exposure of the kidney and retroperitoneal region, we contemplated using the thoracoabdominal incision. This type of incision in its present form is relatively new. One reason for this is that for its safe performance intratracheal anesthesia with the ability to exert positive pressure on the lung is essential, and this advance in anesthesia has come into use only during the past fifteen years. General knowledge concerning the handling of thoracoabdominal wounds and the use of thoracoabdominal incisions was given a great impetus by the surgical experiences of World War II. During the war one of us (L. S.) removed several traumatized kidneys by this route, which was also utilized by others.[1, 2] Although the thoracoabdominal incision has not come into general frequent use, in the last few years it has been used for gastrectomy and esophagectomy for carcinoma,[3-5] for splenorenal anastomosis[6] and for splenectomy.[7] In the light of this knowledge, we decided to make a trial of this incision for the removal of large kidney tumors, and performed our first nephrectomy by this route in January, 1948. (Although Mortensen,[8] of Australia, had removed a large tumor in this manner in June, 1946, we were quite unaware of this, since his case report had not yet been published.)

The excellent exposure that was found to be afforded by this approach greatly facilitated nephrectomy in these difficult cases and led to much enthusiasm on our part, our first few cases being reported in May, 1948.[9] Further experiences with the incision, which has now also been employed with success by several colleagues, have only served to increase our liking for it, and it has now been used in 39 cases for urologic surgery. Twenty of these operations were for renal tumors, and 12 were for the exploration or removal, or both, of kidneys suspected of tumor (mostly large solitary cysts). This procedure has also been utilized to allow nephrectomy when the usual approach to the kidney was blocked by the ribs owing to extreme kyphosis or scoliosis of the spine (2 cases). Furthermore, the particularly excellent exposure of the retroperitoneal region from the diaphragm down that can be obtained by this approach has led to its use, by extension of the incision downward toward the pubis, for retroperitoneal dissection of the lymph nodes along the aorta, vena cava and iliac vessels in cases of carcinoma of the testis (5 cases), and for complete nephroureterectomy in another case, in which the tumor of the renal pelvis involved the ureter. These other uses of the incision in urologic surgery are not discussed further, this communication being confined to a description of the experiences with this approach in the 20 cases of kidney tumor.

The discouragingly low incidence of five-year (15 to 19 per cent) and ten-year (7 to 9 per cent) cures[10, 11] of malignant kidney tumors is obviously due to their high degree of malignancy, coupled with the frequently insidious nature of their onset, especially the renal-cell carcinoma-hypernephroma cases, which comprise the majority of these tumors. In this group the blood supply is very rich, and the malignant tissue is in intimate contact with the vascular spaces, and often parts of the tumor actually project into the blood stream. Thus it is that distant metastases from these tumors

*From the Massachusetts General Hospital.
Presented at the annual meeting of the American Urological Association, Los Angeles, California, May 16, 1949.

†Instructor in surgery, Harvard Medical School; associate visiting urologist, Massachusetts General Hospital; attending urologist, Veterans Administration Hospital, West Roxbury, Massachusetts.

‡Instructor in surgery, Harvard Medical School; assistant surgeon, Massachusetts General Hospital; consulting surgeon, Veterans Administration Hospital, West Roxbury, Massachusetts.

§Assistant in urology, Massachusetts General Hospital.

take place via the efferent blood vessels, such as the renal vein. Local lymphatic metastases to the regional lymph nodes, the nearest of which are located in the region of the renal pedicle and along the nearby anterior aspect of the aorta and vena cava, also occur. Therefore, it is not surprising that many patients die of metastatic disease despite removal of the primary tumor, sometimes succumbing even ten years after nephrectomy. A contributing unfavorable factor is the fact that the patient often is not operated on until the disease is in an advanced stage, either on account of the frequent absence of symptoms until late in the disease or because such symptoms as hematuria have been disregarded. It is indicative of the high malignancy and insidious onset of the tumors that at operation only 8 of the 20 patients in this series were found to have no evidence of extension of the disease outside the kidney, despite the fact that many had had symptoms for only a short time.

It also seems very probable that some of the late distant metastases that not infrequently follow the removal of malignant kidney tumors are due to the fact that particles of tumor have been literally squeezed into the blood stream by the manipulations of the operator while he is freeing up a large vascular tumor preparatory to its removal. Thus, ideally, the surgeon performing a nephrectomy in these cases should interrupt the connection of the kidney tumor with the systemic circulation by clamping the renal vein before he handles the tumor and massages malignant tumor emboli into the blood stream. In addition, such a nephrectomy, to be an adequate operation for cancer in accordance with modern concepts of cancer surgery, should also remove — en bloc with the tumor, if possible — regional lymph nodes and also all the perinephric fat and capsule of Gerota, if possible. Such a procedure is analogous to the dissection of the axillary lymph nodes en bloc with the breast in a radical mastectomy for carcinoma. The ability to perform this type of nephrectomy, which, in our opinion, may prove to be an important step in improving the results of the surgery of these malignant tumors, very largely depends on an exposure wide enough to facilitate its easy and safe performance.

The thoracoabdominal incision furnishes the wide exposure needed. It neutralizes the barrier of the bony thoracic cage, inside which the kidney largely lies, by means of creating surgically a broad pathway directly through it right to the kidney. This gives an exposure of this organ and its pedicle that is direct and wide and definitely superior to that afforded by either the lumbar or the transperitoneal approach in our opinion and that of our colleagues who have used it.

When malignant renal tumors are large, and especially when there are involved lymph nodes adherent to the great vessels in the region of the pedicle or when there is invasion of the inferior vena cava by tumor thrombi, their removal may be exceedingly difficult and dangerous, and sometimes impossible. In such difficult cases the difference between success or failure may depend on whether or not there is good exposure and room to carry out delicate and exacting surgical procedures. As a result of the wide-open approach conferred by the thoracoabdominal incision, both the ease and the safety of the removal of renal neoplasms have been greatly increased, since, even with the largest tumors encountered, the vessels of the pedicle have been fairly easily discovered, and exposed and ligated individually under direct vision. This has decreased the liability to such accidents as uncontrollable hemorrhage and injury to the vena cava, spleen, colon or duodenum, which have sometimes occurred in the past, usually when the surgeon was working in cramped quarters in a deep wound with inadequate exposure and imperfect visualization of important structures. In such cases a lumbar or transperitoneal incision had often been made as long as it was possible to make it, but limitations inherent in the type of incision had resulted in an exposure that was still inadequate for the condition the surgeon was contending with. Those who have operated upon these large vascular tumors under such difficult and unpleasant circumstances will easily appreciate the great value of an exposure that affords both plenty of room and good vision.

As a corollary, it is not surprising that this exposure has allowed the extirpation of large carcinomatous kidneys whose removal had been attempted by another approach but found impossible. In one of our cases a large tumor, whose removal had been attempted unsuccessfully via the lumbar approach by an experienced urologic surgeon, was taken out successfully ten days later via the thoracoabdominal route. The case reported by Mortensen[8] had also been attempted unsuccessfully by the conventional route. In another of our cases in which the thoracoabdominal approach was successfully employed, a huge kidney was found to be very adherent to the vena cava for a distance of about 5 cm. and had to be dissected off with great care; it seems quite certain that the kidney could not have been removed by any other approach without serious damage to the vena cava. Several other tumors in our series probably could not have been removed successfully through any other incision. In this connection, it is significant that in only 1 of these 20 neoplasms, some of which were very large and adherent with local extension, was the kidney not removed. In this case widespread local extension of the malignant lesion seemed to contraindicate any attempt at nephrectomy.

Another technical advantage conferred by this wide-open exposure is that, by facilitating the early ligation of the vessels of the renal pedicle before very much manipulation or freeing-up of the kidney is necessary, it largely avoids the bothersome

and often dangerous hemorrhage from the large veins that run over the surface of some of these large renal tumors. It is believed that these veins are often the result of venous stasis and engorgement secondary to obstruction of the renal vein by a tumor thrombus, and that this back pressure accounts for the fact that they bleed so profusely.

By this route, enlarged regional lymph nodes at the renal pedicle and along the vena cava and aorta were removed in 6 cases. In 4 of these, the removed lymph nodes showed malignant spread, but in 2 cases they surprisingly showed no disease. Two other patients had tumors projecting into the renal vein that were successfully removed. In another case the vena cava was opened and part of its wall excised to remove a tumor thrombus going down it for 1 cm. and adherent inside it. In another case the vena cava, which was involved by direct extension from a malignant tumor of the right kidney, was ligated just below the left renal vein, and a section of it removed with the tumor. As yet, we have encountered no cases with direct extension to the diaphragm, spleen, duodenum or colon, but we believe that if this situation were encountered, resection of the involved portions of those structures might prove feasible. One tumor of the left kidney had already metastasized to the liver, and a tumor on the right had extended directly into the liver. In the latter case the porta of the liver was involved, and although the kidney was removed, it was believed that the disease in the liver was inoperable. However, if the direct extension had been to a more peripheral region of the liver, resection of the involved portion might have been possible. At the time of operation, 1 patient had already had his arm amputated for a metastasis to the humerus, and 2 patients were known to have pulmonary metastases. In view of the occasional cure of a patient with one solitary metastasis by its removal followed by the extirpation of the primary tumor,[12] the renal neoplasm of the first was removed in the vain hope of a chance of cure, and nephrectomy was performed on the latter 2 for the relief of hematuria and pain.

This incision has been performed on both sides, but somewhat more often on the left side than on the right. On the right, even with very large kidney tumors and with somewhat enlarged livers, the overhanging anterior edge of the liver has been easily retracted upward out of the way, and has not interfered with the performance of the operation.

Owing to the fact that the chest wound is held widely open by the rib retractor, less muscular relaxation is needed, and therefore less ether is used than when a comparable operation is performed through the abdominal musculature alone. This can be an important consideration in older and poor-risk patients.

The patients varied in age from one year (a baby boy with a large cystic teratoma) to seventy-seven years, and 5 patients were over seventy. Two of these had severe cardiac conditions, compensated only on limited activity, and 3 others had electrocardiographic evidence of coronary sclerosis. Despite these limitations, with the exception of a woman of seventy-seven whose heart decompensated temporarily one week after operation, the postoperative recoveries were uneventful and the length of the postoperative hospital stay was the same as that for uncomplicated lumbar nephrectomies.

In these 20 thoracoabdominal operations for kidney tumor there has been no operative mortality or death in the hospital. Also, there have been no pulmonary emboli or cases of chest or peritoneal infection. (These statements are also true for the total of 39 thoracoabdominal urologic operations performed to date.) There were only 2 significant postoperative complications, both of which were due to intrapleural hemorrhage. The first hemorrhage was minor, and the chest cleared after one thoracentesis. The second case continued to ooze intrapleurally, probably from torn pulmonary adhesions, and required several chest taps, as well as blood transfusions, during the first few days after operation. Eventually, the blood in the chest became so thick and clotted that it could not be removed, and it bound down and collapsed the lower and middle lobes of the right lung, making an open surgical decortication necessary. The patient, who was seventy-five years of age, tolerated this procedure well and went home in good condition. There were no other postoperative complications.

Thus, it can be seen that we, as well as our colleagues, have experienced a minimum of complications from the thoracoabdominal incision. We are firmly convinced that the important advantages that it confers through the wide exposure are well worth the added effort of the necessarily more complicated operative procedure and of the more exacting preoperative and immediate postoperative care. Also, whereas at first this approach was suggested only for kidney tumors that were obviously large, with further experiences and in view of the good possibility that local extension will be found at operation on any kidney tumor, it is our opinion that one must always be prepared for extensive surgery in every case with the best possible exposure, and that therefore all renal tumors should be operated upon by the thoracoabdominal route.

At the present time, the series of cases is too small and the length of follow-up study far too short to permit any true appraisal of end results, but the operative technic facilitated by this incision should improve the chances of cure and the end results. The patient who could not be operated on died within a few months, and the patient who had nephrectomy and amputation of the arm for what was hoped to be a solitary metastasis is now dying of widespread metastases to the spine, ribs and lungs. In addition, 6 patients, 2 of whom were

known to have pulmonary metastases before operation, have demonstrable metastases to which they will eventually succumb. The other patients are living and apparently well.

The following cases illustrate the problems that occur and show why all renal tumors should be operated upon by the route giving the best possible exposure.

Case Reports

Case 1. A 59-year-old man, previously in excellent health, noticed bloody urine for the first time in his life and had colicky pains from passing clots. After 10 days of this he entered the hospital, where the diagnosis of a tumor of the right kidney was made after x-ray study, even though no mass could be felt. He was operated upon by the lumbar route, and the tumor was found to be so large, to lie so high and to be covered by large veins that bled so profusely that, after a prolonged attempt to free it up, it was considered inoperable and the wound closed. Eleven days later, on account of continuing intractable hemorrhage and colic, the kidney was approached by the thoracoabdominal route and easily exposed. It was found that there was a tumor thrombus about 1.5 cm. in diameter filling the renal vein and extending retrograde downward inside the vena cava for 1 cm. After temporary tension tapes had been applied to the vena cava above and below to control bleeding, the vena cava was opened and it was found that the tumor thrombus had invaded the wall of the vena cava near the entry of the renal vein. The involved portion of the wall of the vena cava was excised and removed with the thrombus and renal vein, after which the kidney was easily removed. The incision in the vena cava was sutured longitudinally with fine silk, and the patient made a very satisfactory recovery. So far he has remained in excellent health for the 4 months since his operation. The microscopical diagnosis was renal-cell carcinoma.

Case 2. A frail, 77-year-old woman with a poor heart entered the hospital with a 3 weeks' history of colicky pain in the right-kidney region associated with episodes of hematuria. She had lost weight, felt tired and had dyspnea on exertion. Examination showed her to be extremely anemic. A large hard mass, which did not move much, was felt in the right-kidney region. After the anemia had been remedied by multiple transfusions, the patient was operated upon through a thoracoabdominal incision. A huge kidney was found adherent to the liver and the duodenum. It was dissected off these structures, but then it was found that the tumor intimately involved much of the circumference of the vena cava. Since this was below the entrance of the left renal vein, the vena cava was tied off here, and a segment of vena cava removed with the tumor, as well as some involved nodes. After a somewhat stormy convalescence, marked by oliguria for some days and also by cardiac decompensation, the patient made a satisfactory recovery. The microscopical report was squamous-cell carcinoma.

Case 3. A 67-year-old man had had cardiac decompensation 3 years previously. After several weeks of bed rest and digitalization he recovered enough cardiac compensation and reserve to be able to get along fairly well on limited activity. For 6 months he had noted an occasional streak of blood in the urine, and 3 days before admission he had noticed definitely bloody urine, with some aching in the left flank. Examination showed a moderate-sized, rather fixed mass high up in the left upper quadrant, and pyelograms indicated a good-sized tumor of the left kidney. After a few days of cardiac preparation with digitalis, a low-salt diet and quinidine immediately before operation, thoracoabdominal nephrectomy was carried out. A large renal tumor was found, and after preliminary ligation of the renal vein and artery, an egg-sized mass of metastatic lymph nodes in continuity with the lower pole of the kidney and extending downward along the anterior surface of the aorta was gently dissected free and removed en bloc with the kidney (Fig. 1). The patient made an uneventful recovery, having no cardiac embarrassment, and when last examined and given x-ray study

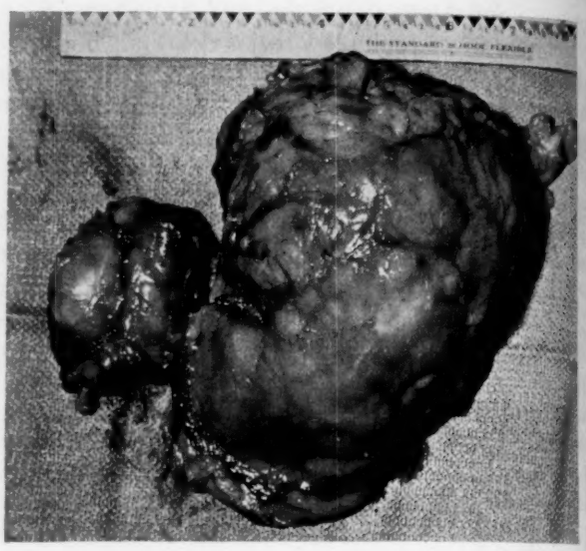

Figure 1. *Kidney Tumor, with Attached Metastatic Nodes Removed en Bloc. (Note That All the Surrounding Fatty Capsule Is Removed with the Kidney.)*

14 months later was well, with no evidence of metastases. Microscopical examination revealed renal-cell carcinoma with extension to the lymph nodes.

Operative Technic

In preparation for the operation of thoracoabdominal nephrectomy, particular attention is paid to increasing the hemoglobin and red-cell count to normal. Older patients and all who have cardiac abnormalities are seen by a cardiologist, and most of these are put on a low-salt diet; some are digitalized, and almost all are given quinidine preoperatively. If the nephrectomy is to be on the left side, a Levine tube is placed in the stomach immediately before operation, to prevent gastric distention, which can be troublesome in operations on that side.

Under intratracheal oxygen-ether anesthesia, the patient is placed on the operating table with the side to be operated upon uppermost. The incision starts about 1 cm. lateral to the spinous processes of the spine in back and runs forward and downward over the entire course of the tenth (or eleventh) rib (Fig. 2). When the end of the rib is reached, the incision is continued in the same direction across the abdominal wall as far as the lateral border of the rectus muscle. The incision is deepened through the muscle layers to the rib, which is removed in its entirety subperiosteally, being resected between its posterior angle and the spine (Fig. 3). It is im-

portant to resect the rib as far back toward the spine as this, because, if it is resected farther forward, the ligaments binding it to the rib above and the rib below will prevent the optimum spread of

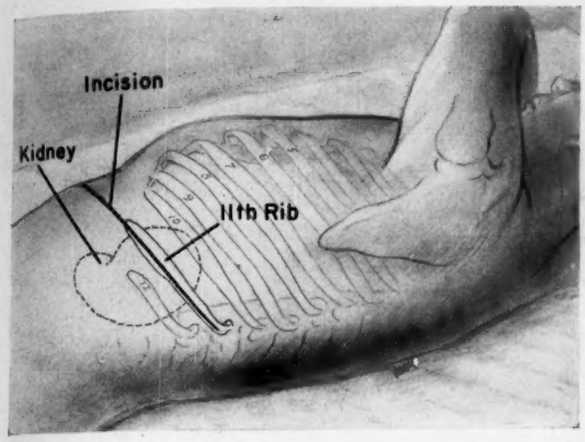

FIGURE 2. *Schematic Drawing, Showing the Location of the Incision in Relation to the Kidney.*

this posterior angle of the wound, which is essential to the maximum possible exposure from this incision. The pleural cavity is entered through the periosteal bed, great care being taken not to injure the underlying lung (Fig. 4). There is less

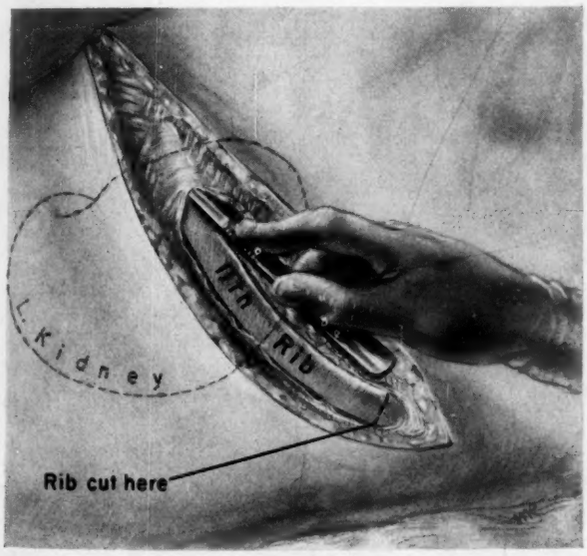

FIGURE 3. *Drawing Showing the Incision for Left Nephrectomy, Starting from Near the Spine in Back Running Forward and Downward over the Left Eleventh Rib and Continuing to the Outer Border of the Left Rectus Muscle.*
The rib is being cleaned preparatory to subperiosteal resection.

chance of doing this if the pleural cavity is opened anteriorly over the diaphragm. The anesthetist is notified when the pleural cavity is entered. Unless adhesions are present, the lung collapses considerably on opening of the pleural cavity and retracts upward. If adhesions between the lung and the parietal pleura or the diaphragm are obvious and in the way, they are gently separated by sharp dissection, great care being taken to secure complete hemostasis with fine-silk ties or ligatures. During the operation, the lung can be walled off by moist gauze, and the anesthetist may keep it almost completely expanded. By retracting the chest wall up and the diaphragm down, one can see the phrenic nerve as it courses downward over the pericardium, and it may be crushed with a hemostat at the point where it leaves the surface of the pericardium to enter the diaphragm. This paralyzes the diaphragm and stops its motion, so that it interferes less with

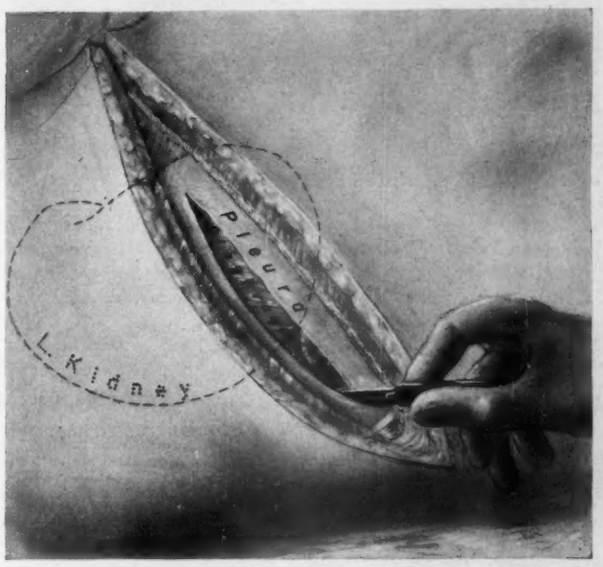

FIGURE 4. *Drawing Showing the Left Pleural Cavity Being Entered through the Periosteal Bed of the Left Eleventh Rib. Care is taken not to wound the underlying lung.*

the operation. The paralysis lasts for about four to six weeks, and the resulting immobility is thought to aid the healing of the diaphragm. However, if the patient has a low vital capacity and it is desirable for him to have the positive muscular action of the diaphragm return soon to help him with respiration, the phrenic nerve is simply injected with a few cubic centimeters of 2 per cent procaine solution, which allows its action to return in an hour or two, and this precaution ensures better postoperative aeration of the lung above. In some cases the phrenic nerve has not been touched, and the motion of the diaphragm has not seemed to interfere with the renal surgery. The diaphragm is then incised in line with the skin incision, the incision also being carried through the peritoneum, which is adherent to its undersurface. Care is taken to avoid cutting into any organ that may be adherent to its underside, such as the kidney tumor, or the

liver on the right side, and the spleen or colon on the left side (Fig. 5). The incision in the diaphragm is carried forward through the decussation of the diaphragm with the transversus abdominis muscle

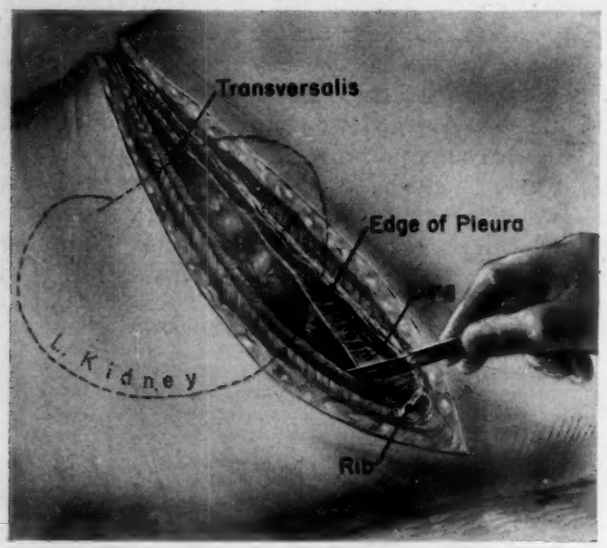

FIGURE 5. *Incision through the Diaphragm and Underlying Peritoneum Carried Forward through the Transversalis and Oblique Muscles to the Outer Border of the Left Rectus Muscle. Care is taken not to injure underlying organs, such as the spleen, kidney and colon.*

and, of course, through the oblique muscles as far as the outer border of the rectus muscle, thus opening the peritoneal cavity widely (Fig. 6). A Finochietto rib retractor is used to separate the ribs,

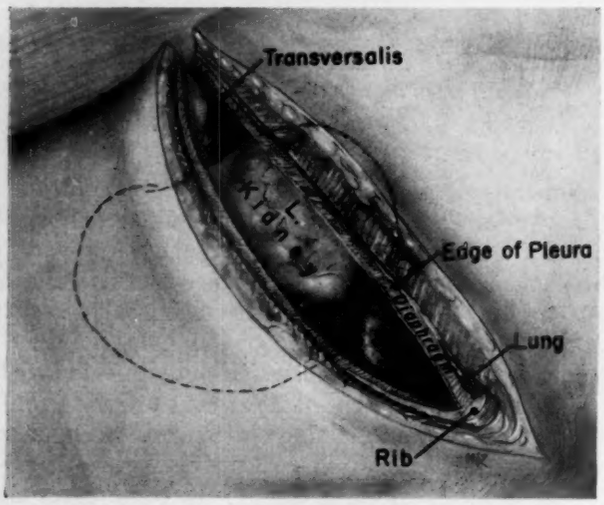

FIGURE 6. *Drawing Showing the Peritoneal Cavity Widely Opened.*

and the kidney then bulges up into the wound (Fig. 7). On the right side the liver also presents, but even if it is somewhat enlarged, it is easily retracted upward out of the way. On the left side the spleen presents and, if it is in the way, it is packed off upward. The renal tumor, surrounded by its intact fatty capsule, is gently retracted laterally, the

FIGURE 7. *Photograph Taken at Operation, Showing the Wound Spread Widely with a Rib Retractor, and the Tumor of the Left Kidney Bulging up into the Wound of Its Own Accord. As yet it has not been freed up at all. The spleen is packed away above.*

duodenum or colon, according to whether the operation is on the right or left side, is gently and carefully freed from its medial aspect, and the renal

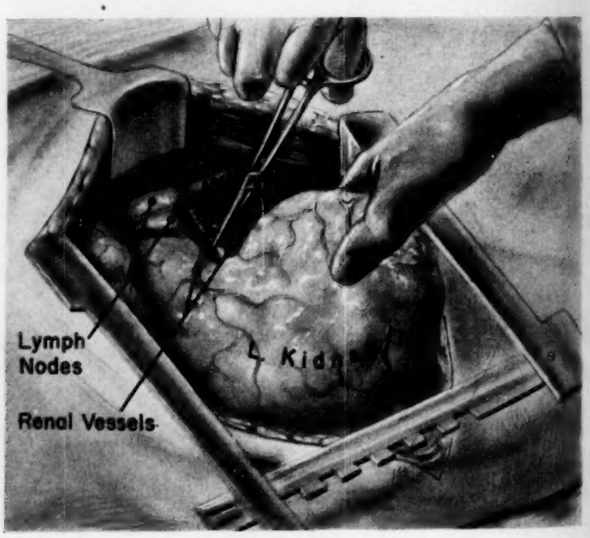

FIGURE 8. *Drawing Showing the Tumor Being Gently Retracted Laterally and the Colon Easily Separated from Its Anterior Medial Surface. The vessels of the renal pedicle are secured individually under full vision. Metastatic lymph nodes along the aorta will be removed with the kidney.*

vein is easily exposed and may be dissected out cleanly (Fig. 8). The dissection of the pedicle is then continued under direct vision, and when the

main renal artery is exposed, the vein and the artery are individually clamped, sectioned and doubly ligated — as well as any smaller vessels found.

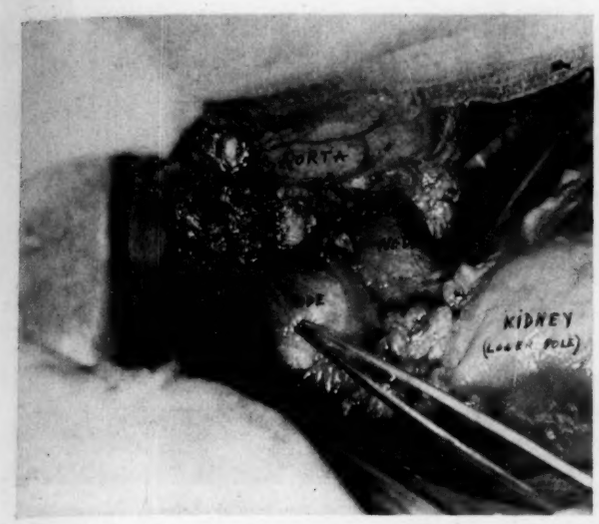

FIGURE 9. *Photograph Taken at Operation, Showing Metastatic Lymph Nodes Dissected from the Aorta en Bloc with the Kidney.*

In addition to the perinephric fat, all lymph nodes and areolar tissue in the region of the pedicle or adherent to the great vessels are dissected away —

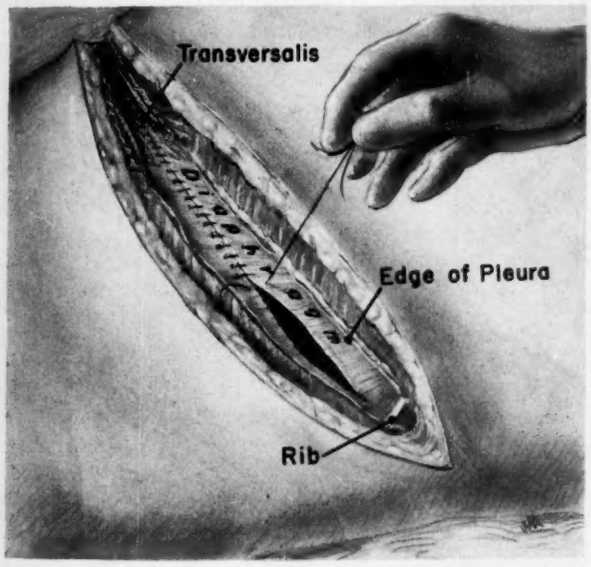

FIGURE 10. *Drawing Showing Wound Closure.*
The anterior part of the peritoneum, from the outer border of the rectus muscle to the diaphragm, has already been closed. The drawing shows the suturing, with interrupted silk stitches, of the diaphragm and of the transversalis muscle, with which it decussates to form a continuous muscle layer for the purposes of closure.

being removed en bloc with the tumor, if possible (Fig. 9). The ureter is sectioned and ligated, the cut ends being carbolized. After this, it is a simple matter to complete the mobilization of the kidney and remove it. If there is direct extension to some neighboring structure such as the diaphragm, it is quite possible that enough of this structure can also be excised to eradicate this extension of the malignant process. After the kidney has been removed, a few stitches may be taken to cover the raw area with peritoneum and to fix the bowel back in position. Then the opening in the peritoneum is closed anteriorly as far back as the diaphragm, a continuous suture of plain O catgut on an atraumatic needle being used. When the diaphragm is reached, it is sutured with interrupted stitches of heavy silk (No. 2) (Fig. 10). Before the chest is closed, 1.5 cc. of eucupine in oil (a long-lasting local anesthetic) is injected hypodermically into the intercostal nerve of the rib resected, and also into the nerve of

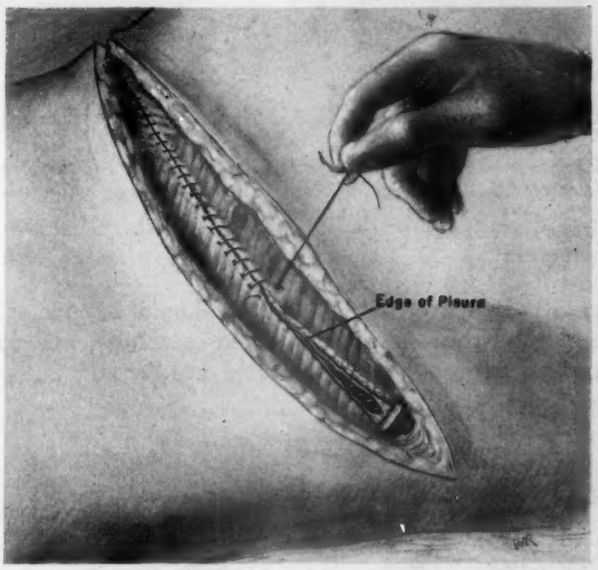

FIGURE 11. *Drawing Showing Closure of the Pleura and of the Muscles in Layers with Interrupted Silk Sutures.*

the rib above and below. This is done inside the chest behind the angle of each rib. It tends to prevent postoperative neuritic pain in the area of the operation, and thus also helps to reduce voluntary "splinting" of the chest after operation with decrease of respiratory exchange. The pleura is reapproximated with interrupted silk sutures. The last two sutures are placed but not tied until the lung has been completely re-expanded by the anesthetist. The muscles are closed in layers with interrupted sutures of No. 3 silk throughout, and the skin is closed with silk (Fig. 11). An alternative method of closing the pleural cavity is to place a No. 18 catheter in the pleural cavity and close the pleura and wound about it, bringing the catheter out in a slanting manner. When the wound is all sutured except the skin, the anesthetist re-expands

the lung with positive pressure, suction is applied to the catheter to empty the pleural cavity, and then the catheter is withdrawn. Great care is taken not to prick the lung with the needle while the pleural cavity is being closed. If this should happen, the edges of the wound should be carefully approximated with a fine atraumatic needle and suture.

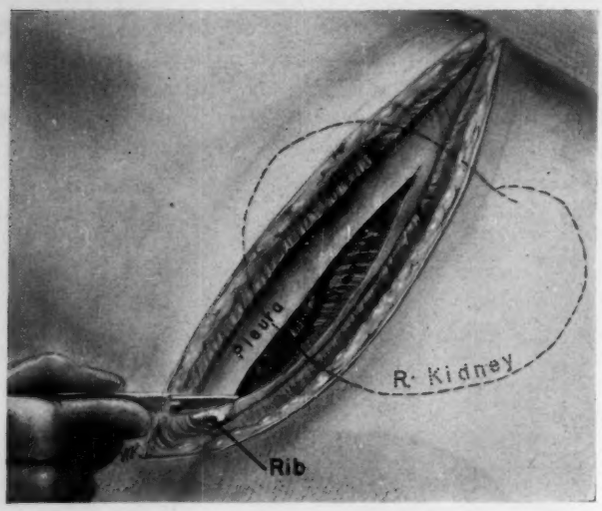

FIGURE 12. *Drawing Showing a Similar Technic on the Right Side.*

The tenth or eleventh right rib has been removed, and the pleura is entered through the bed of the rib, care being taken not to injure the lung underneath.

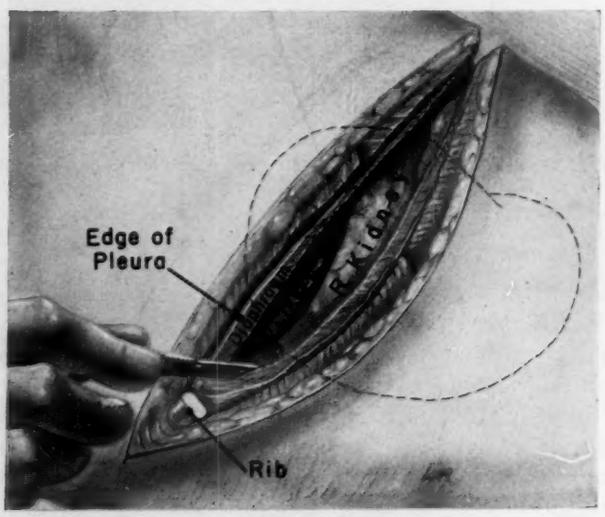

FIGURE 13. *Drawing Showing the Incision of the Diaphragm and Underlying Peritoneum, Care Being Taken Not to Injure the Underlying Liver or Kidney.*

However, if the lung still leaks air on the application of positive pressure by the anesthetist, the chest must be drained. This must also be done when there is persistent oozing of blood into the pleural cavity. If there is any doubt, it is always wiser to drain. Drainage is achieved by means of a No. 22 Foley catheter with a 30-cc. bag inserted through a tiny stab wound in the chest wall two interspaces above the incision, in the axillary line. The catheter should not be led out through the main incision, since this interferes with healing. Its bag is inflated, and the catheter is tied off and brought against the chest wall. It is secured by a skin stitch as well. The chest catheter is connected to three-bottle chest-suction drainage

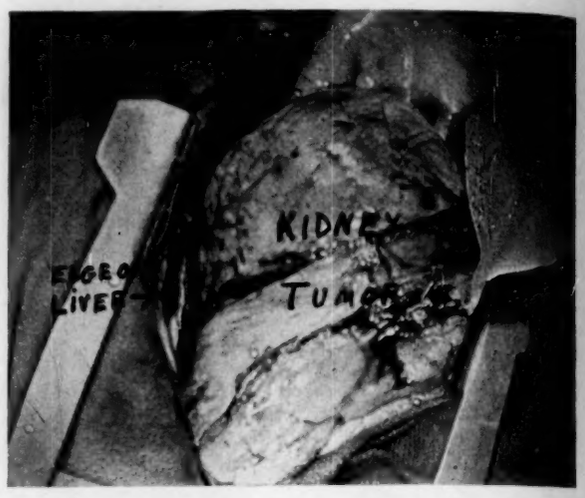

FIGURE 14. *Photograph Taken at Operation, Showing the Tumor of the Right Kidney Presenting of Its Own Accord.*

As yet it has not been freed up at all. The liver is easily retracted upward out of the way.

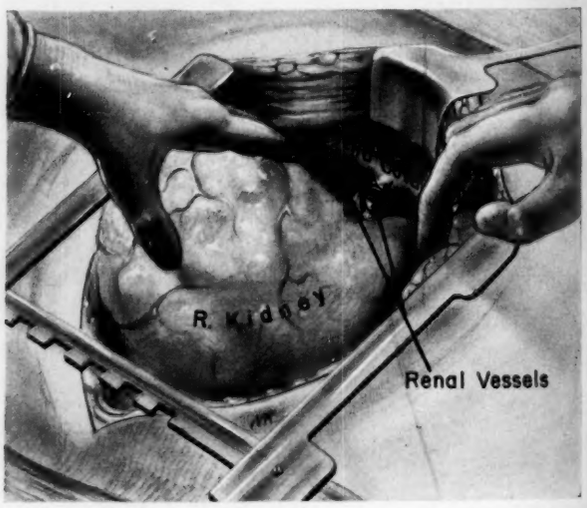

FIGURE 15. *Drawing Showing the Tumor of the Right Kidney Being Gently Retracted Laterally, and the Duodenum Easily Separated from Its Anterior Medial Surface.*

The vessels of the renal pedicle are secured individually under full vision. The liver is easily retracted upward out of the way.

at 8 cm. of negative pressure for forty-eight hours. Thereafter, if there is no further indication for its use, it is removed and the wound immediately covered with a vaseline-gauze dressing to prevent an air leak. A transfusion of 1000 cc. of whole blood is given at the time of the operation. Thereafter, blood is given only as indicated, and is usually not necessary.

The technic on the right side is similar (Fig. 12-15).

Postoperatively, the patient is managed as a chest case. The quinidine and penicillin, with digitalis, if necessary, are continued. Streptomycin in addition may be necessary if the type of bacterial contamination from the kidney warrants it. The patient is turned every hour from his operative side to his back to help avoid atelectasis. Oxygen is given by nasal catheter until there is good aeration of both lungs. This may be for several days, but is usually only for twelve to twenty-four hours.

FIGURE 16. *Photograph Showing the Healed Wound Ten Days after Operation.*

This method provides a fair concentration without interfering with the care of the patient as a tent does, or bothering him as a mask does. The Levine tube is attached to suction for a day or two. Morphine should be administered early and frequently, particularly in patients with coronary-artery disease, for by lessening pain it aids depth of respiration, and diminishes the combination of pain and anoxia that leads to undue restlessness postoperatively and may favor coronary occlusion. Care must be taken to give it in amounts that will not depress the respiratory rate unduly. Intravenous administration of fluids is performed slowly without saline solution (except when such a solution is specifically indicated), unless the patient is young and his cardiac status is good. The patient is allowed up usually on the first postoperative day, and is ready to go home in about ten days as a rule (Fig. 16).

SUMMARY

The thoracoabdominal approach has been used in 39 cases for urologic operations — in 20 for kidney tumors (19 nephrectomies) and in 12 for the exploration or removal, or both, of kidneys that were suspected of being malignant but turned out to be benign (usually large solitary cysts). In 2 cases it has been utilized to allow nephrectomy when the usual approach to the kidney was blocked by the ribs in kyphosis or scoliosis of the spine. In addition, by extending the lower end of the incision downward toward the pubis, it has been used for retroperitoneal dissection of the lymph nodes in the region of the kidney pedicle and along the aorta, vena cava and iliac vessels in 5 cases of carcinoma of the testis, and for complete nephroureterectomy in 1 case in which the tumor of the renal pelvis involved the ureter.

The experience with this incision in the surgery of 20 cases of renal tumor is discussed.

It is our opinion and that of our colleagues that the thoracoabdominal incision affords a much wider and better exposure of the kidney and its vascular pedicle than the extraperitoneal lumbar or the transperitoneal approach.

This wide-open exposure confers the following advantages: greater ease and safety in securing the vessels of the renal pedicle; less manipulation of the kidney before the renal vessels are secured, thereby minimizing the probability of squeezing malignant tumor emboli into the blood stream; increased ability to remove all the perinephric fat and capsule of Gerota with the kidney; increased ability to remove large and extensive kidney tumors, some of which have been found inoperable by another approach; increased ability to remove the malignant extension of renal tumors to the inferior vena cava or to regional lymph nodes, thus constituting a more adequate operation for cancer (such extensions were removed en bloc with the kidney in several cases); and, by early ligation of the renal vascular pedicle, elimination to a large extent of the bothersome and often dangerous hemorrhage from large veins that run over the surface of some kidney tumors.

Because the chest wound is held widely open by the rib retractor, less muscular relaxation is needed, and therefore less ether is used than when a comparable operation is performed through the abdominal musculature alone.

In these 20 thoracoabdominal operations for kidney tumor there has been no operative mortality or death in the hospital. Also, there have been no pulmonary emboli or cases of chest or peritoneal infection. (These statements are also true for the total of 39 thoracoabdominal urologic operations performed to date.) There have been only 2 complications, both of which were due to intrapleural hemorrhage. The first was minor, requiring only one thoracentesis, but the second was major, requiring several paracenteses for the removal of blood, as well as transfusions, and eventually a surgical decortication of the lung. The patient made a satisfactory recovery.

The patients varied in age from one year to seventy-seven years, and 5 patients were over seventy. The cardiac status of several of the patients was not good, and yet the postoperative recoveries were excellent, with the exception of a woman of seventy-seven who had temporary cardiac decompensation one week after operation.

Three case reports are presented.

This series is too small, and the length of follow-up study far too short to permit any true appraisal of end results, but the operative technic facilitated by this incision should improve the chances of cure and the end results.

On account of the excellent operative results with a minimum of complications and the frequency and unpredictability of local extension of malignant lesions of the kidney, the thoracoabdominal incision is recommended for all kidney tumors. We are firmly convinced that the important advantages that it confers are well worth the added effort of the necessarily more complicated operative procedure and of the more exacting preoperative and immediate postoperative care.

The technic of the operation and the preoperative and postoperative care are described.

We are indebted to Dr. Fletcher H. Colby for his encouragement in this work, and to him and to Drs. Wyland F. Leadbetter and George Gilbert Smith for permission to include some of their cases in this series.

References

1. Marshall, D. F. Urogenital wounds in evacuation hospital. *J. Urol.* **55**:119-132, 1946.
2. Wylie, R. H., Hoffman, H. L., Williams, D. B., and Rose, W. F. Thoraco-abdominal casualty. *Ann. Surg.* **124**:463-478, 1946.
3. Sweet, R. H. Transthoracic gastrectomy and esophagectomy for carcinoma of stomach and esophagus. *Clinics* **3**:1288-1315, 1945.
4. Humphreys, G. H., II. Approach to resections of esophagus and gastric cardia. *Ann. Surg.* **124**:288-300, 1946.
5. Garlock, J. H. Combined abdominothoracic approach for carcinoma of cardia and lower esophagus. *Surg., Gynec. & Obst.* **83**:737-741, 1946.
6. Linton, R. R., Jones, C. M., and Volwiler, W. Portal hypertension: treatment by splenectomy and splenorenal anastomosis with preservation of kidney. *S. Clin. North America* **27**:1162-1170, 1947.
7. Carter, B. N. Combined thoracicoabdominal approach with particular reference to its employment in splenectomy. *Surg., Gynec. & Obst.* **84**:1019-1028, 1947.
8. Mortensen, H. Transthoracic nephrectomy. *J. Urol.* **60**:855-858, 1948.
9. Chute, R., and Soutter, L. Thoraco-abdominal nephrectomy for large kidney tumors. *J. Urol.* **61**:688-696, 1949.
10. Deming, C. L. Prognosis and problems in renal tumors. *J. Urol.* **55**: 571-582, 1946.
11. Mintz, E. R., and Gaul, E. A. Kidney tumors: some causes of poor end results. *New York State J. Med.* **39**:1405-1411, 1939.
12. Barney, J. J. D. Twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. *J. Urol.* **52**: 406, 1944.

SYPHILIS IN PREGNANCY*

A Clinical Study of Factors Responsible for Congenital Syphilis

Albert Heyman, M.D.,† and John R. McCain, M.D.‡

ATLANTA, GEORGIA

THE incidence of infantile congenital syphilis has decreased considerably in the United States during the past two decades; nevertheless, cases continue to appear in significant numbers in most city hospitals.[1] Approximately 77 living infants with congenital syphilis have been treated at Grady Memorial Hospital in the past four years. Since congenital syphilis is preventable, it is necessary to inquire into the reasons for its continued occurrence.

Although several articles on factors influencing the outcome of syphilis in pregnancy have been published, the criteria for diagnosis of infantile congenital syphilis in many of these studies are no longer accepted. Thus, in the largest study reported that of the Clinical Cooperative Group,[2] the "information regarding transmission of syphilis to the child was limited to that obtained at birth." Similarly, in the study by Gammeltoft,[3] a diagnosis of congenital syphilis was made when the "child as well as its mother gave a positive reaction, even in the absence of an eruption." Since the serologic test of both the umbilical-cord blood and that obtained in the neonatal period has been shown to have a limited diagnostic value, the accuracy of conclusions concerning the factors responsible for congenital syphilis in these studies is open to question.

Not only has the sensitivity and specificity of serologic tests for syphilis improved since the publication of these papers, but also many of the roentgenographic criteria for the diagnosis of congenital syphilis have undergone considerable modification. The presence of bismuth deposits or nutritional changes in the long bones, for example, was frequently misinterpreted as congenital syphilis.

For these reasons a reconsideration of factors responsible for congenital syphilis seems advisable. This paper presents a review of the syphilitic infection and therapy of the 77 mothers of the infants with congenital syphilis who were treated at the Grady Memorial Hospital in the past four years.

*From the Departments of Medicine and Obstetrics, Grady Memorial Hospital and Emory University School of Medicine, and the Clinic for Genitoinfectious Diseases, Georgia Department of Public Health.

†Associate in medicine. Emory University School of Medicine; visiting physician, Grady Memorial Hospital; director, Clinic for Genitoinfectious Diseases, Georgia Department of Public Health.

‡Associate, Department of Obstetrics and Gynecology, Emory University School of Medicine; member, Visiting Staff, Grady Memorial Hospital.

Method of Study

The majority of the 77 women had prenatal care in the obstetric clinic or were delivered in this hospital. Eleven of them, however, had been attended and delivered by private physicians or had had no prenatal care and were delivered at home.

Detailed information regarding the maternal syphilitic infection was obtained in an interview with the patient, with special emphasis on the duration of the maternal infection, the results of all the patient's serologic tests and the amount of treatment received during and previous to pregnancy. Data regarding syphilitic infection in marital partners and other children were elicited whenever possible. Supplementary data were obtained from the hospital records, the city or county venereal-disease clinics, the State serologic laboratories and the patients' private physicians.

The diagnosis of congenital syphilis in the infants was based upon clinical findings, repeated quantitative serologic tests for syphilis, spinal-fluid studies, dark-field examinations and roentgenographic examination of the long bones. Approximately 80 per cent of the children showed what we consider to be definite roentgenographic evidence of osseous syphilis — that is, osteochondritis of the medial upper portion of the tibia, osteomyelitis and epiphysitis.[4] Considerable care was taken in the interpretation of the serologic tests. No infant with latent syphilis was included in this study unless the serologic tests were found to be persistently positive in high titer. Almost all the patients in the group were infected before birth, since most of them showed overt manifestations of syphilis either at the time of delivery or very early in the neonatal period. Some of them, however, may have acquired syphilis by contact with infectious lesions at the time of delivery or in the early neonatal period.

Negative Serologic Tests for Syphilis in Pregnancy

Several of the earlier studies on prenatal syphilis have shown that women with negative serologic tests in pregnancy may bear syphilitic children.[2] The low sensitivity of serologic tests was thought to be the cause of the negative serologic reaction in most of these patients, particularly in those with long-standing infections and previous therapy. With the increased sensitivity of serologic tests in recent years, such cases have become infrequent, and most workers now believe that women with persistently negative serologic tests will not bear syphilitic children.

Twenty-one patients in this study were known to have a negative serologic test in pregnancy and nevertheless delivered syphilitic children. In only 3 of these 21 patients was insensitivity of the Kahn and Kolmer tests considered to be the cause of a negative reaction. These 3 women had a history of previous therapy for syphilis, and all of them continued to show negative, doubtful or very low titers in the absence of further treatment. The remaining 18 patients with negative serologic reactions in pregnancy demonstrated high serologic titers by the time of delivery or one or two weeks post partum. We believe that these 18 patients either were in the incubation period of the disease at the time of the negative test or acquired an initial or recurrent syphilitic infection later in pregnancy. Cutaneous manifestations of early syphilis were found in 5 of them at delivery or immediately post partum. Six of the 18 patients had been treated for syphilis prior to conception. Thus, a third of the patients in this series in whom syphilis developed during pregnancy had either a reinfection or a relapse of a previous infection, the remaining two thirds having contracted syphilis for the first time. The possibility that a technical error was the cause of negative serologic tests in pregnancy in these 18 patients is considered unlikely, since almost all of them gave a history of having had other negative serologic tests prior to conception. Moreover, the reactions to both Kolmer and Kahn tests were negative during pregnancy in 14 of the 18 patients.

The presence of active syphilis in the patients with negative serologic tests in pregnancy was not suspected, and no treatment was given before delivery. The diagnosis was made when a routine serologic test was obtained during labor or when the infection was suspected in the child. The lesions of early syphilis did not appear during pregnancy or were so inconspicuous as to have been overlooked by both the patient and the attending physician. Although pregnancy is generally believed to suppress the early lesions of syphilis, it does not produce a reduction in the titer of serologic tests or cause false-negative reactions.[5] The diagnosis of syphilis in pregnancy could have been made in almost all these women if repeated serologic tests had been taken throughout the period of gestation. Only 2 women had a negative serologic test for syphilis at the time of parturition; both showed a high serologic titer within three months of delivery. The children of these 2 patients may have acquired syphilis before delivery during the incubation period of the maternal infection, or they may have been infected post partum. These children were not found to have syphilis until five to seven months of age, when they showed roentgenographic evidence of periostitis of the long bones.

The fact that clinic patients often acquire syphilis during the late stages of pregnancy has been noted by Beerman[6] and Goodwin and Farber.[7] These workers have emphasized the importance of repeating serologic tests during the last months of gestation to detect the presence of syphilis acquired

late in pregnancy. This practice, however, has not been a routine procedure in Grady Memorial Hospital. If followed, it should have permitted prevention of syphilitic infection in approximately 20 per cent of the children in our series. Although the need for repeating negative serologic tests in pregnancy is generally recognized, many physicians believe the procedure to be impractical, especially in large obstetric clinics. Repeated tests, particularly in the last eight weeks of gestation, are absolutely necessary, however, if the incidence of congenital infection among a clinic population with a high rate of syphilis is to be reduced to a minimum.

Duration of Maternal Syphilis and Outcome of Pregnancy

It has been observed that women with early syphilis are more likely to bear syphilitic children than those with late syphilis. Nevertheless, there are numerous reports of transmission of congenital syphilis as long as ten to twenty years after the mother acquired the disease. Although most of these reports are not well authenticated, conservative opinion holds that antisyphilitic therapy should be given during each pregnancy, regardless of the duration of the maternal infection.

Information regarding the duration of syphilis in the patients in our study was based chiefly on serologic tests and dark-field examinations made in this hospital or in the venereal-disease clinics. Most of the patients had attended the hospital clinics for many years, and a number of routine serologic tests had been taken prior to their pregnancies. The results of these tests and the clinical history of syphilis as obtained from the patient enabled us to determine with reasonable accuracy the duration of syphilis in 57 of the 77 patients. It was noted that 53 of the 57 patients in whom the duration of the disease could be determined had acquired syphilis or an infectious recurrence less than five years before delivery of the syphilitic child. This information was based on a definite record of negative serologic tests within five years previously or on a positive dark-field examination during that period. Fourteen of the 53 patients had acquired an initial syphilitic infection as long as eight years or more before delivery of the syphilitic child. These 14 patients, however, received sufficient treatment to produce a negative serologic test within four years prior to delivery, and then had either a relapse of the initial infection or a reinfection that was transmitted to the infant.

Only 4 patients were *known* to have a persistent infection for more than five years prior to the birth of a syphilitic child. This information is based on a record of a positive serologic test five or more years before delivery. Two of these 4 patients had had syphilis more than six and seven years before delivery and were among those discussed above as having had negative and doubtful serologic reactions in this pregnancy resulting from insensitivity of the tests. The remaining 2 women with late syphilis had acquired the infection about seven and eleven years previously and had never received treatment prior to delivery of the infected child. The fact that patients such as these, with late syphilis, can deliver infected children, appears to support the current practice of treating syphilis in pregnancy regardless of the duration of the disease.

Treatment before Pregnancy and Outcome of Pregnancy

The pregnant syphilitic woman has always been regarded as a potential source of infection for the fetus, even though she may have had sufficient treatment to prevent the transmission of the disease to her marital partner. For this reason, retreatment of syphilis in pregnancy has been advised regardless of the amount of therapy the patient may have received previously. Recently, this concept has been questioned, and antisyphilitic therapy in pregnancy has been deliberately omitted in a series of selected patients who had had what was considered adequate arsenical or penicillin therapy prior to pregnancy. Goodwin and Farber[7] have reported the outcome of pregnancy in 385 patients, 22 of whom had been treated with penicillin alone. These patients have been observed through 570 pregnancies, none of which resulted in a syphilitic infant. The adequacy of penicillin in protecting the fetus from syphilitic infection in subsequent pregnancies has also been studied by Ingraham and his associates,[8] who found that none of 52 women treated for syphilis before, but not during, pregnancy delivered syphilitic children. These workers emphasized that the patients in whom treatment in pregnancy is to be omitted should be carefully selected and that constant observation should be made during pregnancy for evidence of serologic or infectious relapse.

Approximately three fourths of the 77 women in our study had not received any treatment for syphilis before the pregnancy that resulted in a syphilitic child. Only 5 patients were thought to have had "adequate" treatment before pregnancy; 4 of these had been given from 16 to 32 injections of an arsenical and bismuth preparation each, and 1 patient had been treated with more than 2,000,000 units of penicillin. In all 5 women, however, the syphilitic infection recurred (manifested by either infectious lesions or serologic relapse) just prior to or during the pregnancy that resulted in a syphilitic infant. None of the women had received any treatment for the recurrent infection before pregnancy.

It appears, therefore, that the interpretation of what constitutes "adequate" therapy before pregnancy depends not so much upon the amount of treatment administered as upon the course of the disease after therapy. Treatment of syphilis

during pregnancy can probably be withheld with safety *provided* one can be absolutely certain that a positive serologic test in pregnancy represents seroresistance of an infection that has been adequately treated and not a recurrent syphilitic infection. This differentiation is often very difficult. Many workers attempt to differentiate on the basis of the height of the serologic titer, but this is not always helpful, since a low titer does not always indicate seroresistance and a high titer does not necessarily mean a recurrent infection. Complete data regarding the syphilitic infection are necessary, and information should be obtained regarding not only the amount and type of therapy received but also the duration of the syphilitic infection before treatment, the status of the patient's marital partner and children, and the changes in serologic tests before conception and during pregnancy. If any doubt exists about the interpretation of these data, retreatment during pregnancy should be instituted.

Treatment During Pregnancy and Outcome of Pregnancy

A minimal amount of arsenical therapy given during pregnancy has been claimed to be effective in the prevention of congenital syphilis. McKelvey and Turner[9] have reported that the administration of 12 to 14 injections of an arsphenamine to syphilitic women during pregnancy resulted in noninfected infants in 100 per cent of their cases. It was with some surprise, therefore, that we found that several of our patients had delivered syphilitic children, even though they had received as many as 20 injections of arsenoxide (Mapharsen) in pregnancy. Half, or 16, of the 32 women who were treated in pregnancy had 11 or more injections of Mapharsen; 9 of these had 16 to 20 injections. Only one of these 16 patients, however, began treatment before the fifth month. This patient had 9 injections of Mapharsen early in pregnancy, became delinquent for ten weeks during the sixth to the eight month, and then received 11 more injections in the last five weeks of pregnancy. It should be emphasized, therefore, that although 10 to 20 injections of arsenoxide are often sufficient to protect the fetus of a syphilitic woman, this amount is not always adequate, particularly when given in the last half of pregnancy. The number of syphilitic children in this series born of mothers who had had what is generally considered "adequate" arsenical therapy in pregnancy is further evidence that this form of treatment should be replaced by penicillin.

Most workers now believe penicillin to be the drug of choice in prenatal syphilis. This form of therapy is not only more effective than arsenicals but also relatively nontoxic and can be given in a short period. Furthermore, it is valuable during the last trimester of pregnancy, a time when arsenical therapy is least useful. Penicillin has been shown to be effective in the last few days of gestation, even when the child is already infected. We have observed a case in which delivery occurred on the seventh day of penicillin therapy after the patient had received 4,000,000 units of the drug in aqueous solution.[10] The infant had a strongly positive serologic test and showed definite evidence of osseous syphilis by roentgenographic examination. The lesions of the long bones healed spontaneously, and the Kahn titer became and remained negative without further therapy, indicating that the child had received sufficient penicillin before birth for the infection to be cured. Similar cases have been reported elsewhere.[11] It must be emphasized, however, that penicillin is not uniformly successful for patients treated late in pregnancy. We have observed 2 patients, not included in this series, who were treated in the last trimester and delivered syphilitic, stillborn infants immediately after penicillin therapy. Death of the fetus was apparently caused by an overwhelming syphilitic infection.

In the present study only 1 patient who had completed the course of penicillin therapy during pregnancy delivered a syphilitic child. This patient received 4,800,000 units of crystalline penicillin G in aqueous solution during the fourth month of pregnancy. At that time the serologic test was positive with 40 Kahn units, and she had secondary syphilis. The Kahn titer fell to 4 units three weeks before parturition, but rose to 40 units two days before the syphilitic child was born, and before retreatment could be instituted. A recurrence of the maternal infection prior to delivery, as in this case, is one of the causes of congenital syphilis in infants born after penicillin therapy. Although it is infrequent, such a possibility should be kept in mind. Serologic tests should be taken at monthly intervals throughout pregnancy, and possibly more frequently near term. Retreatment with penicillin should be given during pregnancy if there is any doubt of the possibility of infectious or serologic relapse.

Discussion

This study was stimulated by an attempt to determine the reasons for the large number of syphilitic infants delivered in or referred to this hospital. The presence of negative serologic tests in pregnancy and the inadequacy of arsenical therapy were responsible for the infection in two thirds of these infants. A number of other factors are believed to be of great importance in the transmission of congenital syphilis. Foremost among these is the failure of clinic patients to come for prenatal care early in pregnancy. One fourth of the 77 patients in this series did not receive any treatment during pregnancy because they came to the hospital just prior to or after the beginning of labor. Still others received inadequate therapy because they sought prenatal care late in pregnancy

or became delinquent after a few treatments. Although the use of penicillin in such patients would have prevented some of the congenital infections, there is no doubt that the prevention of congenital syphilis is largely a matter of public-health education. Women should be urged to seek prenatal care early in pregnancy.

In a few cases the attending physician did not establish the diagnosis of syphilis sufficiently early or did not institute immediate or vigorous antisyphilitic therapy. Several of our patients were attended by private physicians, who neglected to take blood for serologic tests.

Summary

A clinical study of the factors responsible for the transmission of infantile congenital syphilis was made by a review of the records of 77 women who delivered syphilitic infants.

Approximately a fourth of these women had negative serologic tests for syphilis in pregnancy and, for this reason, had not received any prenatal treatment for syphilis. The majority of these patients are believed to have been in the incubation period of the disease at the time of the negative test, or to have acquired an initial or recurrent syphilitic infection later in pregnancy. The importance of repeating serologic tests near term to detect syphilis acquired late in pregnancy is emphasized.

The duration of the maternal infection was almost always less than five years prior to birth of the syphilitic infant. An occasional patient transmitted syphilis to her child even though she had had the disease for as long as eleven years previously.

Half the women who were given prenatal treatment had received 11 to 20 injections of arsenoxide during pregnancy. The inadequacy of arsenical therapy given late in pregnancy is pointed out. Penicillin therapy is believed to be the treatment of choice in prenatal syphilis and will probably result in a considerable reduction in the incidence of congenital infection.

The most important measure, however, in the prevention of congenital syphilis is greater education of pregnant women, who should be urged to seek prenatal care early in pregnancy.

References

1. Barker, L. P. Evaluation of penicillin treatment in early congenital syphilis. *J. Pediat.* **32**:516-521, 1948.
2. Cole, H. N., et al. Cooperative clinical studies in treatment of syphilis: syphilis in pregnancy. *Ven. Dis. Inform.* **17**:39-46, 1936.
3. Gammeltoft, S. A. Syphilis and pregnancy. *Am. J. Obst. & Gynec.* **15**:747-757, 1928.
4. Weens, H. S., and Heyman, A. Cited in *Recent Advances in the Study of Venereal Diseases: A symposium.* 341 pp. Raleigh, N. C.: Venereal Disease Education Institute, 1948. P. 341.
5. Crosby, E. L., and Campbell, A. D. Quantitatively titered serologic test in early syphilis and its response to treatment. *Am. J. Syph., Gonor. & Ven. Dis.* **25**:566-582, 1941.
6. Beerman, H., and Ingraham, N. R., Jr. Recent advances in management of syphilitic pregnant woman. *M. Clin. North America* **29**: 1463-1476, 1945.
7. Goodwin, M. S., and Farber, M. S. Necessity for treatment of pregnant syphilitic women during every pregnancy. *Am. J. Syph., Gonor. & Ven. Dis.* **32**:409-417, 1948.
8. Ingraham, N. R., Jr., Rose, E. K., Stokes, J. H., and Beerman, H. Retreatment of pregnant woman for syphilis following penicillin: is additional therapy necessary when effective treatment has been given prior to conception? *Am. J. Obst. & Gynec.* **56**:340-346, 1948.
9. McKelvey, J. L., and Turner, T. B. Syphilis and pregnancy: analysis of outcome of pregnancy in relation to treatment in 943 cases. *J. A. M. A.* **102**:503-510, 1934.
10. Cross, J. B., McCain, J. R., and Heyman, A. Use of crystalline penicillin G in treatment of syphilis in pregnancy. *Am. J. Obst. & Gynec.* **57**:461-465, 1949.
11. Tucker, H. A. Penicillin syphilotherapy administered during pregnancy: study of 149 pregnancies during which penicillin was given for early maternal syphilis. *Am. J. M. Sc.* **217**:157-161, 1949.

THROMBASTHENIA AND THROMBOCYTOPENIC PURPURA*

Report of Case Demonstrating Qualitative and Quantitative Inadequacy of Platelets

BENJAMIN ALEXANDER, M.D.,† AND GRETA LANDWEHR, S.B.‡

BOSTON

RECENT advances in the knowledge of blood coagulation clarify understanding of the hemostatic defect underlying various hemorrhagic disorders. The pathogenesis of hemorrhagic disease is usually attributable to disturbed retractility of the small blood vessels, as in vascular and allergic purpura; thrombocytopenia; deficiency of antihemophilic "globulin" — hemophilia§; insufficiency of prothrombin or its accessory factors — for example, hypoprothrombinemia, parahemophilia,[2] deficiency of prothrombin A[3] and accelerator globulin deficiency[4]; fibrinopenia; and presence of circulating anticoagulants — heparin[5] or heparin-like substances.[6]

There are, however, clinical conditions in which the nature of the hemostatic dysfunction is obscure, such as those designated as "hereditary hemorrhagic thrombasthenia"[7] and "pseudohemophilia."[8, 9] Glanzmann[7] ascribed hemostatic failure in his subjects to a qualitative abnormality of the platelets because of their bizarre appearance and delayed clot retraction. Von Willebrand and Jürgens[8] also described platelet abnormalities in their patients, and concluded that the hemorrhagic phenomena were due to defective platelet agglutinability.

The purpose of the present communication is to report data in a patient with pseudohemophilia that demonstrate that the hemorrhagic tendency was associated with a qualitative defect in the patient's platelets despite their normal number. Subsequently, the patient developed thrombocytopenia suggesting a possible relation between purpura of the Glanzmann and von Willebrand type and idiopathic thrombocytopenic purpura.

CASE REPORT

A 40-year-old married truck driver (P.B.B.H. 384)¶ was admitted to the Peter Bent Brigham Hospital on March 27, 1949, because of hemorrhage. One month before, he had noted bleeding from the palate, gums and nose, and expectoration of blood-streaked sputum. Six days prior to admission he experienced coryza and slight cough, and observed small red spots on his leg. He took several "four-way cold tablets" (aspirin, quinine, magnesium hydroxide and phenolphthalein). He was also aware of easy bruising and some hematuria. Except for a bilateral epistaxis 2½ years before admission there had been no hemorrhagic phenomena.

The family history revealed no bleeding tendency in the parents, or in 3 sisters and 1 brother.

At age of 18 the patient had gonorrhea, and he remembered an indurated, painless "cold" sore on his lip that could have been a chancre. After the incidental discovery of a positive serologic test in 1943 he received 4 courses of Mapharsen and 5 courses of bismuth. In 1945, because of a persistently abnormal spinal fluid, he was given 10 paroxysms of malarial fever and 13 2-gm. doses of Tryparsamide. There had been no neurologic, cardiac or genitourinary symptoms.

For several years the patient had been taking 1 teaspoonful of "Bismarex" or "Bisodol" daily because of epigastric postprandial distress. (These antacids contain bismuth subcarbonate.) The past history was otherwise irrelevant. There had been no exposure to other drugs or toxic chemicals, and there was no allergic history.

Physical examination revealed a well developed, well nourished man with confluent purpura over the arms, hips and thighs. The pupils were Argyll-Robertson in type. The mouth showed petechial hemorrhages on the hard palate, upper gums and buccal mucosa. The lower gums, which revealed some gingivitis, bled on pressure. There were a few small cervical submandibular and left axillary lymph nodes. The lungs and heart were normal. The liver and spleen were not palpable. Reflexes were normal. The blood pressure was 135/70. X-ray study of the abdomen and bones was negative.

The urine was normal except during the first several days, when the sediment was packed with red cells. Examination of the blood revealed a red-cell count of 4,200,000, with a hemoglobin of 14.1 gm. per 100 cc., a hematocrit of 43 per cent and a normal white-cell count. For the first several days the smears showed abundant platelets.

On March 28 the platelet count was 204,000, the bleeding time (Duke method) 65 minutes and the clotting time 6 minutes (Lee–White method). The clot failed to retract within 32 hours. The prothrombin time was 17 seconds (control, 17 seconds). Capillary fragility (Rumpel–Leede technic) was markedly positive. On April 3 the bleeding time was 25 minutes, and the clotting time 9 minutes; clot retraction again was poor. On April 9 capillary fragility was again markedly increased. On April 13 the platelet count was 8000. On April 23 the bleeding time was 3 minutes, and the clotting time 8 minutes; the clot failed to retract. No platelets could be seen on the blood smear. On April 5 the platelet count was 25,000. A bone-marrow aspirate showed numerous megakaryocytes by direct smear and in fixed section. Two protamine-heparin titration tests were normal.

The stools consistently showed + to ++++ tests for occult blood.

Because he showed progressive clinical improvement despite the thrombocytopenia that developed, the patient was discharged on April 5 to return to the Out-Door Department for further observation. The low platelet count, high bleeding time and increased capillary fragility have persisted till the present time.

Studies of the Coagulation Defect||

Methods. Platelets were counted by the Rees–Ecker method.[10] Recalcification times were determined at room temperature on oxalated plasma (1 part of one-tenth molar sodium oxalate to 9 parts of blood) to which was added one-fifth volume of 1 per cent calcium chloride solution.

Plasma prothrombic activity was determined by the modified one-stage procedure of Rosenfield and Tuft,[11] in which

*From the Medical Research Laboratory, Beth Israel Hospital and the Department of Medicine, Harvard Medical School.
Supported by a grant from the Commonwealth Fund.

†Assistant professor of medicine, Harvard Medical School; visiting physician and associate in medical research, Beth Israel Hospital.

‡Research fellow in medicine, Harvard Medical School; associate in medical research, Beth Israel Hospital.

§It is still uncertain whether hemophilia is referable to a deficiency in antihemophilic "globulin" or to a circulating anticoagulant, anti-cephalin, or both.[1]

¶We are indebted to Drs. Clement Finch and Stuart Finch, of the Peter Bent Brigham Hospital, Boston, for making this case available for study. The data in the case report are from the records of that hospital.

||The data recorded in this section were obtained in the Medical Research Laboratory of the Beth Israel Hospital.

normal plasma rendered prothrombin-free by adsorption with barium sulfate is used as a diluent for the test plasma. Residual serum prothrombic activity was similarly measured on serum from blood allowed to clot spontaneously, or from oxalated plasma that was recalcified.[12] The serum was separated 1 hour after coagulation, oxalated (1 part oxalate to 4 parts serum), and then incubated for 15 to 30 minutes at 37°C. to inactivate thrombin.

Results. On March 29 the patient had 275,000 platelets per cubic millimeter of oxalated plasma (well within the normal range in our laboratory). Plasma prothrombic activity was 90 per cent, whereas the residual serum prothrombic activity (one-stage method) was 130 per cent. This observation, in agreement with those obtained in thrombocytopenia,[13] indicated a distinct coagulation defect despite the normal platelet count and clotting time.

Further studies were done in which the patient's platelets were transferred to deplateletized normal plasma and normal platelets transferred to deplateletized patient plasma. On March 31 oxalated plasma (158,000 platelets per cubic millimeter) from the patient and from a normal subject (182,000 platelets per cubic millimeter) were centrifuged at 15,000 r.p.m. in the multispeed attachment of the International Centrifuge for 15 minutes at 7°C. The supernatant plasmas, carefully separated from the platelet pellets, contained 14,000 and 18,000 "platelets" per cubic millimeter respectively.

TABLE 1. *Abnormal Platelet Function in a Patient with Thrombasthenic Purpura.*

TYPE OF PLASMA	PLATELETS	PROTHROMBIC ACTIVITY		RECALCIFICATION TIME
		PLASMA	SERUM	
	per cubic millimeter	%	%	*min.*
Patient:				
Whole	158,000	90	150	11
Deplateletized	14,000	—	42	30*
Deplateletized plus Normal platelets	235,000	—	0	5
Normal subject:				
Whole	182,000	90	0	6
Deplateletized	18,000	—	30	30*
Deplateletized plus Patient's platelets	167,000	—	15	11

*Approximate values.

The sediments were washed twice with physiologic saline solution. The patient's platelets were then dispersed with vigorous agitation in a volume of platelet-poor normal plasma equivalent to the plasma from which the patient's platelets were derived, giving a mixture with a final platelet count of 167,000 per cubic millimeter. Similarly, the normal platelets were suspended in the patient's plasma, yielding a final count of 235,000 per cubic millimeter. Recalcification times and residual serum prothrombic activities were determined.

The recalcification time of the patient's whole plasma was distinctly greater than normal (Table 1). As anticipated, removal of platelets from both types of plasma retarded coagulation considerably. Addition of normal platelets to the patient's deplateletized plasma restored the recalcification time to normal. In contrast, the recalcification time of the normal plasma containing the patient's platelets was abnormally prolonged, and was the same as that of the patient's whole plasma.

The prothrombic activity of serum obtained from recalcification of the patient's whole plasma exceeded that of the parent plasma, as did serum from the patient's blood allowed to clot spontaneously (as described above). In contrast, serum similarly derived from whole normal plasma showed no prothrombic activity. Recalcification of normal plasma deprived of its platelets yielded serum that contained substantial prothrombic activity. This was somewhat reduced when the patient's platelets were added to the platelet-poor normal plasma. However, serum obtained from a mixture of normal platelets with the patient's platelet-poor plasma was devoid of prothrombic activity just as serum obtained from whole normal plasma.

The following additional observations were made: on April 4 the patient's platelet count was 212,000 per cubic millimeter of whole blood, and plasma prothrombic activity was 106 per cent, whereas residual serum prothrombic activity was 95 per cent. On April 7 the plasma contained 84,000 platelets per cubic millimeter. The patient's residual serum prothrombic activity was still elevated (80 per cent of the parent plasma). On April 11 the platelet count was 57,000 per cubic millimeter of capillary blood and 50,000 per cubic millimeter of oxalated venous blood.

The accelerating effect of the patient's plasma on the coagulation of blood from a patient with known hemophilia was normal. This helped exclude a diagnosis of hemophilia.

It is thus evident that early in the course of the disease, despite the normal platelet count, the patient's blood showed the following evidence of defective coagulation: prolonged recalcification time and high serum prothrombic activity. This could be rectified completely by the addition of normal platelets to the patient's deplateletized plasma, whereas the patient's platelets could not correct the abnormality induced in normal plasma by removal of its platelets.

Within 2 weeks of admission thrombocytopenia developed and has persisted until the present.

DISCUSSION

Although the role of platelets in the hemostatic mechanism is not entirely understood, certain facts have been clearly established. Reduction in platelet number is associated with hemorrhagic phenomena, prolonged bleeding time, abnormal clot retraction and disturbed capillary retractility. Also, a clotting defect has recently been demonstrated in spontaneous thrombocytopenia and in blood from which the platelets are artificially removed: coagulation is retarded,[14] prothrombin consumption is reduced, and residual prothrombic activity in the serum is elevated.[13, 15] This is in accordance with the general opinion that the platelets are required for the elaboration of thromboplastin.

The degree of thrombocytopenia necessary to induce the clinical and laboratory manifestations of purpura varies from patient to patient,[16] and suggests that qualitative differences in the platelets are important. Furthermore, the existence of normal platelet counts in cases demonstrating many features commonly associated with thrombocytopenic purpura raises suspicion that the quality of the platelets in these subjects may be poor.

The observations in the case reported above indicate that such aberrations in platelet function actually occur. Early in the course of his disease the patient showed the salient clinical manifestations of thrombocytopenic purpura despite normal platelet counts: bleeding into the skin and from the mucous membranes, increased bleeding time, normal clotting time, increased capillary fragility and poor clot retraction. Although this case may have been unique these features justify a diagnosis of "thrombasthenia" or "pseudohemophilia," since in this syndrome the platelet count is usually normal, the bleeding time is variable, the clotting time of venous blood may be normal or increased, clot retraction is usually normal but may be poor, and capillary fragility may be normal or markedly increased. The absence of a bleeding tendency in

the family does not exclude this interpretation since in many cases a positive family history cannot be elicited.[9]

The experimental data, obtained during this time, also were like those found in thrombocytopenic purpura — namely, high residual serum prothrombic activity and prolonged recalcification time. Since normal platelets added to the patient's deplateletized plasma rectified this clotting defect, and conversely, addition of the patient's platelets to normal plasma deprived of its platelets did not correct the abnormality thus induced, one must conclude that the patient's platelets were inherently defective and unable to function normally. The addition of normal platelets to thrombocytopenic blood similarly corrects its clotting defect.[13] Thus, except for the normal number of platelets, the patient's blood was indistinguishable from thrombocytopenic blood.

Progression of the disease to thrombocytopenia is of considerable interest. Had the patient been first seen at this point, a diagnosis of idiopathic thrombocytopenic purpura would have been considered correct. It is difficult to relate the underlying condition to the syphilis or to possible acquired sensitivity to bismuth, which the patient had been taking in the form of antacids. The finding of a normal bone marrow containing numerous megakaryocytes helps exclude thrombocytopenia on the basis of chemical destruction.

The sequence of thrombocytopenia following thrombasthenia suggests the possibility that idiopathic thombocytopenic purpura is sometimes preceded, if only for a short time, by abnormal platelets that are removed from the circulation. In this connection, previous observations[13] on a patient with thrombocytopenic purpura treated by splenectomy may be significant. Although the platelet count in this subject returned to normal after the procedure, coagulation was still abnormal, suggesting some qualitative inadequacy of the platelets. She suffered a relapse within a few months.

Means are now available to detect functional abnormality of platelets in patients with hemorrhagic phenomena. The finding of abnormally high residual prothrombin in the serum indicates inadequate conversion of prothrombin to thrombin. A normal plasma prothrombin time will exclude as its cause deficiency of any factor in the prothrombin constellation — labile factor, prothrombin A, accelerator-globulin, factor V or the factor of Fantl and Nance[17] as well as fibrinogen. Subnormal prothrombin conversion can then be referable only to inadequate evolution of thromboplastin that is due to hemophilia, which can be readily excluded, thrombocytopenia, thrombasthenia or circulating anticoagulants. The last is easily demonstrable by the prolonged clotting time as well as the retarding effect of the plasma in question on the clotting time of normal blood or plasma.

No method for precise measurement of the functional capacity of platelets has yet been devised. On the basis of the above observations one might propose the following procedure: addition of the platelets in question to normal plasma, drawn and deprived of its platelets with meticulous precautions against platelet breakdown according to the technic of Brinkhous.[14] The mixture of normal platelet-free plasma with the platelets to be studied could then be recalcified, and residual serum prothrombic activity determined. Normally no prothrombin should be demonstrable. The amount of prothrombin remaining in the serum should be a measure of thromboplastin evolving from the platelets since all other clotting factors important in prothrombin conversion will have been provided or adequately controlled. This method is being evaluated.

Summary

Functional inadequacy of platelets (thrombasthenia) associated with hemorrhagic phenomena occurs. This was demonstrated by observations on a patient with purpura, elevated bleeding time, increased capillary fragility, poor clot retraction, normal platelet count and normal clotting time. He showed a coagulation defect indistinguishable from that observed in thrombocytopenic purpura, reflected in an elevated recalcification time and high residual serum prothrombic activity.

This could be rectified by the addition of normal platelets to the patient's deplateletized plasma, whereas the patient's platelets were unable to correct the coagulation defect induced in normal plasma by deprivation of its platelets.

The platelet count, at first normal, later dropped to thrombocytopenic levels. This suggests a possible relation between thrombasthenia and idiopathic thrombocytopenic purpura.

The detection of thrombasthenia is discussed.

A method for measuring the functional capacity of platelets is proposed.

References

1. Tocantins, L. M. Demonstration of antithromboplastic activity in normal and hemophilic plasmas. *Am. J. Physiol.* **139**:265-279, 1943.
2. Owren, P. A. Parahaemophilia: haemorrhagic diathesis due to absence of previously unknown clotting factor. *Lancet* **1**:446-448, 1947.
3. Quick, A. J. Components of prothrombin complex. *Am. J. Physiol.* **151**:63-70, 1947.
4. Sykes, E. M., Jr., Seegers, W. H., and Ware, A. G. Effect of acute liver damage on Ac-globulin activity of plasma. *Proc. Soc. Exper. Biol. & Med.* **67**:506, 1948.
5. Allen, J. G., and Jacobson, L. O. Hyperheparinemia: cause of hemorrhagic syndrome associated with total body exposure to ionizing radiation. *Science* **105**:388, 1947.
6. Allen, J. G., Bogardus, G., Jacobson, L. O., and Spurr, C. L. Some observations on bleeding tendency in thrombocytopenic purpura. *Ann. Int. Med.* **27**:382-395, 1947.
7. Glanzmann, E. Hereditäre hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen. *Jahrb. f. Kinderh.* **88**: 1, 1918.
8. von Willebrand, E. A., and Jürgens, R. Über ein neues vererbbares Blutungsübel: die konstitutionelle Thrombopathie. *Deutsches Arch. f. klin. Med.* **175**:453-483, 1933.
9. Estren, S., Sanchez Médal, L., and Dameshek, W. Pseudohemophilia. *Blood* **1**:504-533, 1946.
10. Rees, H. M., and Ecker, E. E. Improved method for counting blood platelets. *J. A. M. A.* **80**:621, 1923.

11. Rosenfield, R. E., and Tuft, H. S. Estimation of prothrombin level from prothrombin time. *Am. J. Clin. Path.* **17**:405-412, 1947.
12. deVries, A., Alexander, B., and Goldstein, R. Factor in serum which accelerates conversion of prothrombin to thrombin. I. Its determination and some physiologic and biochemical properties. *Blood* **4**:247-258, 1949.
13. Alexander, B., and deVries, A. Factor in serum which accelerates conversion of prothrombin to thrombin. III. Its relationship to coagulation defect of thrombocytopenic blood. *Blood.* **4**:747-751, 1949.
14. Brinkhous, K. M. Clotting defect in hemophilia: deficiency in plasma factor required for platelet utilization. *Proc. Soc. Exper. Biol. & Med.* **66**:117-120, 1947.
15. Quick, A. J., Shanberge, J. N., and Stefanini, M. Coagulation defect in thrombocytopenic purpura. *J. Lab. & Clin. Med.* **34**:761-767, 1949.
16. Aggeler, P. M., Howard, J., and Lucia, S. P. Platelet counts and platelet function. *Blood* **1**:472-496, 1946.
17. Fantl, P., and Nance, M. Acceleration of thrombin formation by plasma component. *Nature, London* **158**:708, 1946.

ACRIBIA

HENRY J. L. MARRIOTT, M.A., B.M. (Oxon.)*

BALTIMORE

THE practice of medicine is said to be an art as well as a science. Certainly at its best it is a happy blend of both. But today science is nurtured at art's expense, with the unhappy result that doctors are more and more enthralled by numbers and devices, and less and less concerned to cherish precision of their own. Yet this personal precision is as much to be desired as it is sorely lacking, both in clinical skill and in literary expression. The Greeks, as usual, had a word for it, ἀκρίβεια, whose shades of meaning have been well translated "exactness, literal accuracy, precision, niceness of sense." Hippocrates, who called medicine "The Art" (and there was little that one would call "scientific" in his art), emphasized the need for this faculty. This need is as great today as it was yesterday.

With so much in medicine that is still inexact, it is the greater pity that inaccuracies have been allowed to taint the medical vocabulary. When a disease is named, for instance, one should be sure one knows what the adopted word means. Yet "erythromelalgia" has recently been attached uncomfortably to a form of headache. This is as good, or as bad, an example as one can hope to find of the crime that Oliver Wendell Holmes called "verbicide." In this particular case there is less than usual excuse, because Weir Mitchell, in his original description of the disease, adds an explicit footnote to his title, "the foot and hand disorder I am about to describe may be conveniently labeled Erythro-mel-algia; ἐρυθρός, red; μέλος, a member; ἄλγος, pain." Thus the new syndrome, "erythromelalgia of the head," can only mean, if words mean anything, "pain in the red limbs of the head," which is anomalous to say the least. If an affection of the head, analogous to erythromelalgia, is to be given a name, "erythrocephalalgia" is all that is required. Another lapse is the not infrequent use of "anhydrosis" for "absence of sweating." This is a natural enough mistake, supposedly because the writer believes that the word is compounded from the stem hydro- (water); it is of course derived from ἱδρώς (hidros), sweat, and the word is, and has been for 2400 years since Hippocrates used it, anidrosis, or often with the "h" retained, anhidrosis. "Pruritis" is another misbegotten child; the word is pruritus, and has nothing to do with the "-itis" that usually connotes inflammation. Its ending is the same as that in tinnitus and exitus, and it has survived and been used by medical writers since the time of Pliny (70 A.D.). Therefore, it deserves at least the respect of age.

Such inaccuracies may seem trivial, and, indeed, in themselves, they are. But they are a symptom of a too prevalent syndrome, the etiology of which is indifference for literal accuracy, and indeed for any education that aims at "niceness of sense" without being strictly utilitarian. If the matter is given any careful thought, however, there are many apparent reasons why a cultural, nonscientific education, including a more than passing knowledge of the classical languages, is of great and lasting value to physicians. It is an asset that will accumulate interest with the passage of the years. For "the real object of education is to give children resources that will endure as long as life endures; habits that time will ameliorate, not destroy; occupations that will render sickness tolerable, solitude pleasant, age venerable, life more dignified and useful, and death less terrible."

First, and least important, a classical education makes the understanding of medical terms easier and more interesting, and therefore encourages a more exact and careful usage of them.

Secondly, it teaches the English language better than any other form of education. The mental gymnastics that are inevitable (because of the entirely different classical idiom) in construing from Latin and Greek into English, and vice versa, teach one the meaning and use of one's own tongue as nothing else can. The writings of medical men are consistently referred to as "literature," but that dignity is seldom deserved.

Thirdly, the classics are a real education in the sense that they teach one *how* to think. No other training so constantly involves the exercise of judgment. There is always a decision to be made,

*Associate in medicine, University of Maryland School of Medicine.

not between right and wrong, but between good and better, and so discrimination and good taste are continually sharpened and polished by practice. Most serious educators will still agree with the thesis that the main purpose of education is to teach one how to think rather than what to think. Yet modern education seems more and more exclusively to offer opportunities for the simple accumulation of usable facts. Such factual knowledge, without the wisdom to apply it, is of limited value. Osler once made the following penetrating statement:

> After all, the greatest difficulty in life is to make knowledge effective, to convert it into practical wisdom. We often confuse the two, and we think they are identical. But. . . far from being one, they often have no connection whatever.

Wisdom is the result of experience in a man who can profit by it because he has cultivated the ability to use his mind well. Unfortunately for the future, the medical student is a tender plant more often watered with a jet of "scientific method" than with the gentle rain of culture; so knowledge grows while judgment withers.

It is a reflection on the critical faculty of physicians that a spark, kindled in 1928 by Fleming, was allowed to smoulder unheeded for over ten years before it burst into therapeutic flame, and that Mendel's doctrine was allowed to hibernate for thirty years before it saw the light of recognition. Again, the Schemm regime is often thought of as an innovation. It is overlooked that, as Dr. Schemm himself recalls, Sir Thomas Witherly reported in 1690 his winecooper who cured his own prodigious dropsy by ingesting 14 quarts of water in ten hours. Such flowers of progress are left to blush unseen in the dark, unfathomed recesses of the library stacks, while doctors busy themselves about their little, self-important papers, intent on adding their special "gem" to an already embarrassing wealth of publications. They are apt to forget that the empty vessel makes the greatest sound. Such a premium is set on "getting something published" that the journals are too often full of forests of trivialities in which one cannot see true landmarks for the trees.

Finally, a classical education can be of help by giving an interest in a really beautiful study: the study of peoples in their prime, of civilizations at their best, of poetry and drama in their heyday. This may seem flat and unprofitable to the exclusive moneymaker, but it is an interest that time does not destroy. Education is the only worldly possession that cannot be lost until one loses one's senses. Moreover, the average patient prefers to consult a doctor with an education and a soul — and so it has even its material reward.

When the soured, thrombosed moneymaker retires to live on his store of gold, how empty is his existence compared with that of his colleague who has developed "occupations that will render. . . life more dignified and useful." He must either fall into the spinsterly prerogative of minding other people's businesses or else resign himself to stale and weary boredom. As Osler said so well, "You may find too late, with hearts given away, that there is no place in your habit-stricken souls for those gentler influences which make life worth living."

MEDICAL PROGRESS

VITAMIN SUPPLEMENTATION IN HEALTH AND DISEASE*

PERRY J. CULVER, M.D.†

BOSTON

THE importance of vitamins in nutrition has been so forcefully and repeatedly stressed by radio, newspaper and word-of-mouth advertising that the general public is most receptive to the inclusion of vitamin supplements in daily diets. Any report that implies or promises alleviation of chronic or incurable illness by the use of a vitamin preparation excites further demand for vitamins. The magnitude of vitamin consumption in this country is evidenced by the fact that the annual sale of vitamins in the United States amounted to $188,000,000 in 1947.[1] There was a 300 per cent increase (from $15,000,000 to $45,000,000) in the sale of costly, high-potency preparations between 1945 and 1947. The commercial outlets for vitamins[1] showed that a considerable proportion of the sales are for self-prescribed vitamins rather than for those on physician's prescription. Of the total $188,000,000 sales in 1947, $26,000,000 were made through mail-order houses, department stores, grocery stores and variety stores.

That the public is not alone in its intense interest in vitamins is manifest. In the last four years since the subject of vitamins was reviewed,[2] three or four thousand articles covering various aspects of vitamins have appeared in medical journals throughout the world. Among these were several careful surveys of specific topics.

Cowgill[3] presents a conservative but thought-provoking discussion of some of the clinical applications of research in the field of vitamins. Salient points include a consideration of the causes for great individual variation in vitamin requirements; the controversial topic of subclinical vitamin deficiency; the nonspecificity of the so-called signs of vitamin deficiency; and mention of some vitamin interrelations and of antivitamins. Cowgill's paper does not pretend to be encyclopedic; it is, rather, a delightful discussion of some recent advances in the knowledge of vitamins.

A concise, factual tabulation of all the vitamins, with brief outlines of their chemistry, indications and requirements, is presented by Harris.[4] Useful information about the members of the vitamin B complex is completely reviewed by Elvehjem.[5] This paper deserves attention. Gripwall[6] emphasizes subclinical states of vitamin B deficiency and discusses etiologic factors but data to support some of his statements are lacking. In addition, he is inconsistent. He indicates the need for massive doses (20 to 40 mg.) of thiamine and then discusses a case of ariboflavinosis that developed after therapy with thiamine. He appears to recognize vitamin imbalance but does not consider it in his therapeutic advice.

The role of the fat-soluble vitamins is discussed in a brief but fairly complete review by Embree.[7] The history of folic acid up to 1947 and its therapeutic uses are covered by Sargent.[8] One final review is an excellent summary of antivitamins. Wright[9] discusses this complex subject in simple, understandable terms.

In view of the large number of conflicting reports concerning the beneficial effect of various vitamin supplements, another review of the vitamin literature published during the last four years, with emphasis upon vitamin requirements and on the value of vitamin supplements, seems timely. The following questions are considered:

Is there objective evidence to justify such a tremendous use of vitamin supplements?

Does the promiscuous ingestion of vitamins benefit public health or promote recovery from disease?

Can overindulgence in vitamins cause harm beyond deflation of the public pocketbook?

It is difficult to answer these questions without emotional bias. There are increasing manifestations that the vitamin fad is passing and that a more conservative view of their therapeutic value is developing. Several recent reports stress a well balanced diet as preferable to purified vitamin supplements.[3, 5, 6, 10] It is my opinion, however, that as long as the public believes in the magic of vitamins, the physician will be forced to prescribe them, although he may not anticipate any benefit beyond a psychologic one. Moreover, practitioners are carefully informed of all progress in the therapeutic use of vitamins by manufacturers who, for obvious reasons, favor reports that stimulate sales.

In this review, the continued reports on small numbers of well recognized specific deficiency states are not discussed. The results of animal and bacteriologic experimentation are slowly revealing the

*From the Medical Clinics, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School.

†Associate in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.

physiologic role of vitamins, as well as leading to the discovery of new substances, but the limitations of this review permit no more than occasional reference to them. Answers to the questions posed will be approached through the following major subdivisions: standards of minimal and optimal vitamin intake; nutritional surveys and subclinical vitamin deficiency; reports of specific therapeutic uses of vitamins; newer vitamins; toxicity of vitamins; and antivitamins and vitamin imbalance.

Standards of Minimal and Optimal Vitamin Intake

A knowledge of the minimal requirements for the various vitamins is an aid in evaluating the need for wholesale supplementation of the American diet with multivitamin capsules. Commercial advertising frequently stresses a widespread inadequacy of vitamins in food intake. The validity of these claims is open to question when the available information about minimal requirements and limitations of vitamin therapy is reviewed. Opinion varies about what constitutes the minimal requirement for any given vitamin. One theory is that the minimal requirement is the smallest amount sufficient to prevent clinical manifestations of deficiency. This value can be determined for thiamine, vitamin C and, with less certainty for vitamin A, riboflavin, niacin and vitamins D and K — that is, vitamins in whose absence or deficiency specific signs or symptoms of avitaminosis have been recognized in man. In view of the fact that most deficiencies are multiple,[3, 6] the clinical determination of minimal requirements has depended upon the experimental production of a specific deficiency by restriction of that vitamin. An objection to this approach is that such conditions are abnormal and, with thiamine at least, reduction of intake may affect body metabolism and secondarily its thiamine requirement.[11] I believe that such an objection is more theoretical than actual and that determination of minimal vitamin requirement by the experimental production of a clinical deficiency is a valuable technic.

The clinical investigation of requirements for the other known vitamins is limited by the absence of specific signs or symptoms of deficiency in man. Large body stores of some vitamins and endogenous synthesis of others add to the difficulties of establishing the minimal demands.

There are many investigators who believe that the minimal requirement for a vitamin should prevent subclinical deficiency,[3, 12] a state of physiologic and biochemical derangements that cannot be detected clinically.[11] The need for more delicate methods for defining subclinical deficiency has led to biochemical and biologic measurements of blood and urinary excretion levels for some of the vitamins. There is great variation in the analytical methods and little agreement concerning what level of tissue saturation represents the critical point of subclinical deficiency for any given vitamin. I wonder if the biochemical level below which a subclinical deficiency exists varies with the emotional bias of the investigator toward clinical or subclinical deficiency standards and with his enthusiasm for vitamin therapy. Moreover, the blood levels of vitamin A[13] and the urinary excretion values of riboflavin, N-methyl nicotinamide, biotin and folic acid may remain relatively constant for long periods in spite of changes in intake or may fluctuate greatly without correlation with intake or with physical status of the patient.[14-20] For these reasons it is difficult to establish by laboratory methods which levels indicate the minimal requirement of various vitamins necessary to prevent a subclinical deficiency.

Vitamin A

Man has such large stores of vitamin A in his liver[21] that determinations of the minimal requirement by experimental development and prevention of clinical signs of vitamin A deficiency have been difficult and few. On the basis of animal studies, Embree[7] has estimated that the minimal requirement of vitamin A is one tenth of the optimal requirement. If this estimation can be applied to man, the minimal requirement might be 500 to 600 international units per day. By maintaining a normal subject on a vitamin A deficient diet for approximately 598 days, producing a significant fall in the plasma vitamin A level from 133 to 76 I.U., Hartzler[22] found that administration of 2000 to 3500 I.U. of vitamin A per day was sufficient to stabilize the plasma level or even raise it slightly.

Using the maintenance of normal dark adaptation as the end point, another investigation[23] showed that the minimal requirement for vitamin A averaged 40 I.U. per kilogram of body weight in 5 subjects (range, 25 to 56 I.U.). For a man weighing 70 kg. this would require 2800 I.U. of vitamin A. However, many investigators think that the dark-adaptation method is unreliable. These limited studies suggest that any intake above 3000 I.U. of vitamin A per day is adequate, but, in calculating the intake, one must make allowance for the large proportion of unavailable carotene in vegetables.[23]

Thiamine

Studies of minimal requirements have been more extensive for thiamine than for other vitamins, possibly because the symptoms of thiamine deficiency dominate the picture of vitamin B inadequacy.[14] If the minimal requirement is based upon prevention of clinical symptoms, two reports[24, 25] from China and the Philippines agree that 0.4 mg. of thiamine per 1000 calories is the critical level of intake, below which frank beriberi appeared. The re-

quirement in both these reports was probably somewhat higher than that under normal conditions because of poor, unbalanced diets, diarrhea and the increased demands of pregnancy.

On the basis of experimental development of symptoms of thiamine deficiency by restricting the intake at varying levels, Foltz et al.[26] concluded that the minimal daily requirement for young men ranged from 0.33 to 0.45 mg. per 1000 calories. In a carefully controlled study lasting one hundred and sixty-one days, Keys et al.[14] observed that a thiamine intake of 0.185 mg. per 1000 calories, together with restriction of other B vitamins and a 3300-calorie diet, was without significant effect on "fitness," health and personality. After four weeks at this level of intake, there was a O urinary excretion of thiamine. That the body reserves of thiamine were being depleted during this period of restriction was evidenced by the rapid deterioration of these subjects when there was further restriction of the thiamine intake to 0.008 mg. per 1000 calories. The rapidity of this deterioration was striking in comparison with that in a control group that had been receiving a supplement of 1 mg. of thiamine per day before the acute restriction to 0.008 mg. per 1000 calories. On the basis of their studies, Keys et al.[14] are of the opinion that 0.23 mg. of thiamine per 1000 calories is adequate.

In another well controlled investigation with restriction of thiamine to 0.5 mg. per day as well as reduction in the intake of other B vitamins and protein, Berryman et al.[27] observed symptoms of deficiency within fifteen to eighteen weeks. Supplementation with crystalline thiamine alone did not relieve these symptoms. Hathaway and Strom[28] found that 0.84 mg. of thiamine per day allowed 3 women to live symptom-free and with a sense of well-being. Using the reaction-time technic, Tuttle et al.[29] noted no aberration from normal unless the thiamine intake was less than 0.625 mg. per day.

Values for the urinary excretion of thiamine at any given level of intake vary considerably among different observers, and there is an even greater variance of opinion in the interpretation of these results. Zero excretions of thiamine were observed at intakes of 0.5[27] and 0.61 mg. per day.[14] On the other hand, other investigators[20] found some urinary excretion (10 to 29 gamma per day) of thiamine with intakes as low as 0.28 to 0.40 mg. per day. When subjects ingested 0.7 mg. of thiamine per day, Oldham et al.[20] observed a sudden increase in the urinary excretion level to 35 to 78 gamma per day. At a daily intake of 0.84 mg., [28] the urinary excretion was 90 to 112 gamma per day. By some standards this value for urinary excretion is above the lower limits of "normal."

Alexander[11] was dissatisfied with the method of restriction of dietary intake for determining minimal thiamine requirements. Instead, he made a thiamine balance study, which established a minimal thiamine requirement of 0.7 mg. per day on a 2400-calorie diet, or 0.29 mg. per 1000 calories if allowances were made for the urinary excretion of partial breakdown products of thiamine. Holt et al.[30] employed a refinement of the urinary-excretion technic whereby increments of the thiamine intake were added and subtracted until a critical point of minimum urinary excretion was found. The higher excretion rate above this point was believed to represent a surplus above minimum physiologic needs. By this method the minimal thiamine requirement for adults was 0.6 mg. per day, and that for infants was 0.14 to 0.20 mg. per day.

A final biochemical approach to the problem of determining the minimal thiamine requirement was the use of a complex index based upon changes in blood lactic and pyruvic acids after glucose administration and exercise.[31] Subjects with a daily thiamine intake of 0.4 mg. were found to be at the borderline of biochemical abnormality. Probably, a lower level for the minimal thiamine requirement is obtained by this method because the pyruvic acid metabolism seems to remain constant even when the urinary-excretion level of thiamine has reached zero.[14]

In arriving at the value or values for minimal thiamine requirements, one must consider other factors. The generally accepted theory that an interrelation between carbohydrate intake and utilization of thiamine exists is questioned by Keys et al.,[14] who suggest that the actual thiamine requirement may be a constant as well as an amount proportional to the total fat calories and may be somewhat less than 0.61 mg. per day, regardless of calories. This theory is opposed to the common idea that fat spares thiamine. It is unlikely that intestinal synthesis of thiamine plays a role in determining the minimal requirement because thiamine is not absorbed from the colon.[11, 27, 28] Contrary to popular opinion that the demand for thiamine is increased during the consumption of alcohol, an isocaloric substitution of alcohol for carbohydrate resulted in increased thiamine excretion.[32] This was interpreted as indicating a thiamine-sparing action of alcohol.

In a case of an American prisoner of war with severe beriberi, symptoms recurred when he was shifted from parenteral to oral vitamin therapy, but when hydrochloric acid was given in addition, he could be maintained fully on oral intake alone.[33] This observation is merely a clinical impression and is at variance with a better controlled study, which showed no effect of gastric anacidity on thiamine absorption as determined by the urinary excretion level.[34] Other experiments demonstrated that thiamine ingested with meals was excreted

in the urine in twice the quantity excreted when it was taken in equal amounts between meals.[35]

Further investigations indicated that thiamine requirements may be increased for the first week after severe burns or injury, as shown by low urinary excretion in spite of daily intakes of 3 mg. of thiamine.[36, 37] Confirmation of these observations will require further investigation with larger supplements of thiamine to prove that the post-traumatic decrease in urinary excretion is due to increased thiamine utilization and not to other factors. I have not discovered any other controlled studies within the last four years that demonstrate an increased demand for thiamine during various disease states. The apparent effect of an elevated metabolic rate upon increasing thiamine utilization has been summarized previously.[38]

On consideration of all these reports on various investigations into the minimal requirement for thiamine and into the factors that may modify it, it seems justifiable to conclude that an intake of 0.26 to 0.35 mg. per 1000 calories, with consumption of at least 0.7 mg. per day, is a reasonable approximation of the minimal requirement for thiamine.

Riboflavin

The amount of riboflavin required by man to prevent clinical or subclinical deficiency has not been determined with any certainty. During the last four years there have been no reports of success in the experimental production of clinical riboflavin deficiency. Volunteers have lived on 0.3 mg. per 1000 calories for one hundred and sixty-one days[14] and on 0.28 mg. per 1000 calories for more than a hundred days[39] without any evidence of ariboflavinosis. Either a much greater restriction of riboflavin intake or the introduction of other unknown factors is required for the development of the clinical findings characteristic of riboflavin deficiency.

It is impossible to define subclinical deficiency on the basis of the urinary excretion of riboflavin because many factors in addition to the quantity of riboflavin consumed affect urinary excretion. Oldham et al.[40] found that there was a striking inverse relation between urinary riboflavin excretions and nitrogen balances. Under conditions of a constant intake of riboflavin, the urinary excretion varied from 40 to 60 per cent of the intake during periods of strong negative nitrogen balance to only 7 per cent when the subjects were in positive nitrogen balance. These observations confirm and extend the work of Andreae et al.,[41] who showed that there was a retention of 0.3 mg. of riboflavin with each gram of nitrogen retained. Moreover, this nitrogen-riboflavin relation explains the marked fluctuations in riboflavin excretion subsequent to burns and injury[36, 37, 41] and opens to question any statements about the increased requirement for riboflavin after trauma.

There is ample evidence of intestinal synthesis of riboflavin, which can be greatly modified by the type of diet ingested.[42] During periods of low riboflavin intake, fecal excretion of riboflavin may exceed the amount provided in the diet.[39] The demonstration of considerable amounts of "free" riboflavin in the feces suggests the possibility of utilization of riboflavin synthesized in the intestine when oral intake is low.[42] To date no one has proved that the riboflavin from intestinal synthesis is absorbed. In view of these nondietary factors, which may alter the level of urinary excretion of riboflavin, it is surprising to note the agreement of different investigators concerning the correlation of urinary excretion with the quantity ingested when the dietary intake of riboflavin is 1.4 mg. or less.[42] Regardless of the factors that complicate interpretation, there have been attempts to estimate the riboflavin requirement proceeding on the assumption that urinary excretion reflects tissue saturation. Davis et al.[39] found that there was urinary excretion of 40 per cent of the increment in riboflavin intake between 1.02 and 1.23 mg. At higher levels of intake approximately the same percentage of the increment was excreted, whereas at intake levels below 1 mg. very little of the increment was excreted. These findings are interpreted as indicating that there is tissue saturation with riboflavin at an intake of 1.23 mg. per day and that this quantity of the vitamin meets the human requirement. Brewer et al.[43] observed a similar change in urinary excretion of riboflavin when the intake exceeded 1.3 to 1.5 mg. per day. They define this level as the "optimal" intake of riboflavin or upper limit at which there is economical utilization of the substance.

A final comment about the requirement for riboflavin is the change from computing it on the basis of caloric intake to computing it on the basis of 0.020 mg. per body weight.[44] To summarize the observations on riboflavin requirements, I believe that 1.0 mg. per day is more than adequate to prevent subclinical ariboflavinosis.

Niacin

There are very few data about niacin requirements in man. Niacin (nicotinic acid) and nicotinamide are equally effective therapeutically.[45] In practice nicotinamide is preferred because its administration is not associated with the unpleasant side effects caused by niacin. In this discussion, the word niacin refers generically to both substances.

The experimental production of clinical niacin deficiency in man has not been reported. No signs or symptoms of niacin lack were observed in a group that consumed 5.8 mg. per day for fifteen to eighteen weeks.[27] Tissue stores of niacin may be sufficient to meet ordinary demands for long periods and in-

crease the difficulties of producing a state of experimental deficiency.[17] The type of diet also alters niacin requirements. For example, tryptophane acts as a precursor for niacin,[46] whereas the probable presence of an antiniacin factor in corn would increase the need for niacin when corn products are ingested.[47]

Determination of the urinary excretion of niacin or its metabolic derivative N-methyl nicotinamide has little value in establishing requirements for niacin. With intakes ranging from 6.9 to 25 mg. per day in 12 subjects, the urinary excretion of niacin was found to be almost constantly 1.0 mg. per day, and the fecal excretion 1.0 to 1.9 mg. per day.[20] The N-methyl nicotinamide excretion in the urine was observed to be the same with intakes of either 12 or 22 mg. per day.[14]

For lack of better data, the closest estimate to the minimal daily requirement for niacin is 5 mg., with an increase to 7.5 mg. if there are corn products in the diet.[44]

Lesser Known Members of the Vitamin B Complex

There are practically no data on the human requirements for the lesser known members of the vitamin B complex. Specific deficiency states for pyridoxine, pantothenic acid, para-amino benzoic acid, biotin, choline and inositol have not been discovered. Lack of folic acid and vitamin B_{12} may contribute to the development of macrocytic anemias. It is most probable, however, that some of these lesser known or even some as yet unidentified components are essential to adequate human nutrition. This was demonstrated by experiments that showed incomplete recovery or even aggravation of some existing deficiency symptoms when depleted persons were given supplements of crystalline thiamine, riboflavin and niacin only. It was only after restoration of a full diet or addition of brewers' yeast that there was complete relief from all deficiency stigmas.[24, 27]

The few scattered reports on lesser known members of the vitamin B complex are summarized as follows. The production of suggestive pyridoxine deficiency with manifestations of depression, mental confusion and leukopenia was reported to occur within two months on a synthetic diet containing supplements of the other known vitamins in crystalline or purified form, but the quantity of pyridoxine needed to "cure" was not determined.[48] The "burning-feet" syndrome described in a number of nutritional surveys of prisoners of war is attributed to pantothenic acid deficiency.[24, 49] The possibility of pantothenic acid deficiency in man is questionable, however, on the basis of work that revealed excretions to approximate intakes ranging from 2.1 to 4.7 mg. per day.[20] It is suggested either that no pantothenic acid is destroyed in the body or that intestinal synthesis compensates for the destruction in the tissues.[20] A study of human utilization of biotin showed urinary and fecal excretion to be three to six times that of intake, the excess probably coming from intestinal synthesis.[18] Consequently, human biotin deficiency is unlikely. On the basis of animal studies, the human requirement for folic acid is estimated to be 0.1 to 0.2 mg. per day.[44] The hematologic response of patients with Addisonian pernicious anemia suggests that man requires less than 1 gamma of vitamin B_{12} per day.[50]

Any concern about meeting the human requirements for the lesser known members of the vitamin B complex can be allayed when it is known that the ordinary diet supplies these factors in adequate amounts when foods that contain the major components of the vitamin B complex are ingested.[51]

Vitamin C

In contrast with vitamin A and the B complex, the amount of vitamin C required to prevent clinical scurvy has been established with some accuracy,[52] and several investigations have correlated the degree of tissue saturation with the quantity of vitamin C taken in.[53-55]

Investigators from the British Medical Research Council demonstrated, during an observation period of four hundred and twenty-four days, that a daily intake of 11 mg. of vitamin C prevented the development of clinical scurvy.[52] It is possible that an even lower level of intake would prevent scurvy because after 3 subjects had been on an 11-mg. intake of vitamin C for one hundred and sixty days, they were maintained for one hundred and ninety-five days on intakes that were reduced still farther to 3.2 to 4.5 mg. of vitamin C per day without the appearance of clinical signs of scurvy.[52] In 6 cases of clinical scurvy developed during an intake of only 1 mg. of vitamin C per day for seven months, 10 mg. of vitamin C per day effected a slow cure after that period. It is interesting to note that the plasma levels of ascorbic acid fell with the same rapidity and to the same low levels of 0 to 0.05 mg. per 100 cc. both in the group whose daily intake was 1 mg. of vitamin C and in the group that received 11 mg. per day. Although 11 mg. per day prevented the appearance of scorbutic manifestations, this intake of vitamin C did not eliminate such vague symptoms of deficiency as fatigue. To satisfy ill defined additional needs and to allow a margin of safety, it was suggested that a daily vitamin C intake of 30 mg. be regarded as the requirement of a normal adult.[52] This recommendation agrees with the League of Nations daily minimum requirement for vitamin C of 30 mg.[56] and is close to the maximal daily utilization of 30 to 40 mg. found by Crandon et al.[57]

The correlation between plasma vitamin C levels and intake as found by different investigators is summarized in Table 1. The close agreement between the results of Johnstone et al.[54] and Dodds[55]

is striking in view of the long period of maintenance at a given level of intake in one study and the brief period in the other. The lower values and steady decrease observed by Haines et al.[53] are difficult to reconcile with the results of the other two investigations.

Although these biochemical determinations prove a definitive relation between tissue saturation with vitamin C and the level of intake, there is difficulty in establishing the level below which subclinical deficiency occurs. A fasting plasma ascorbic acid level below 0.6 mg. per 100 cc. is considered by some to be the critical level necessary for normal vitamin C metabolism.[54] This would require an intake of approximately 50 mg. of vitamin C per day. Moreover, plasma levels below 0.25 mg. per 100 cc. or intakes below 22 mg. per day are believed to be in the deficiency range.[54, 58, 59] Complete saturation of tissues and white blood cells with vitamin C was found to be accomplished by intakes slightly in excess of 70 mg. per day,[53, 59] but it has never been proved that complete tissue saturation is necessary for optimal health. In fact, as a result of saturation tests, it has been postulated that the body economy is more wasteful of its vitamins when they are in good supply.[60] When fully saturated, the body is estimated to contain 4 gm. of vitamin C.[57, 59] Another approach, which has been introduced by Slobody et al.,[58] is the determination of tissue saturation with vitamin C by the rate of decolorization of dichlorphenol indophenol injections into the skin. As yet, its clinical application has not been tested.

A greatly increased demand for vitamin C in persons with burns and severe injury has been well demonstrated.[36, 37] Experimental studies on wound healing in human subjects depleted in vitamin C[61] have confirmed earlier observations[57, 62, 63] of the need for additional vitamin C to promote development of tensile strength and healing in surgical wounds. The only dissenting report was that of normal healing of experimental wounds with a vitamin C intake of only 11 mg. per day over an eleven-month period.[52]

After considering these reports, I believe that a vitamin C intake of 30 mg. per day is more than adequate to meet the minimal requirements in man except during periods of stress.

TABLE 1. *Relation of Daily Vitamin C Intake to Plasma Level.*

INTAKE mg./day	PLASMA LEVEL* mg./100 cc.	PLASMA LEVEL† mg./100 cc.	PLASMA LEVEL‡ mg./100 cc.
22.3	—	0.26	—
33.0	0.48	—	0.28-0.36
53.0	—	—	0.42-0.63
57.0	0 72	—	—
62.5	—	0.75	—
70.0	—	—	0.50-0.86
78.3	—	0.87	—
82.0	0.93	—	—
107.0	1.05	—	—
400.0	—	1.20§	—
437.5	—	1.49	—

*Data of Dodds and MacLeod.[55] A seven-day to ten-day adjustment period on each intake preceded these plasma values, which represent two-day and six-day averages.

†Data of Johnstone et al.[54] The subjects were maintained for six to nine months at the various levels of intake.

‡Data of Haines et al.[53] The values recorded are those for the sixth week after the beginning of the various intakes, which had been preceded by a saturation period. At each level of intake observed, there was a steady decrease in the plasma level during the six weeks of study.

§Determined after three days at an intake of 400 mg. per day.

Fat-Soluble Vitamins

Vitamin D. The minimal requirement for vitamin D in adults is approximately zero[51]; 400 I.U. of vitamin D is ample for children because this amount produces no greater calcium retention than 800 I.U.[44] An increased demand for vitamin D has been shown in cases of steatorrhea.[64] Oral doses of as much as 12,000 I.U. of vitamin D per day may be insufficient to maintain calcium balance in steatorrhea, but the same quantity of vitamin D administered intramuscularly becomes effective.[65] There have been reports of rare cases in which the absorption of vitamin D was satisfactory but in which clinical rickets, resistant to the normal quantity of vitamin D, required 150,000 to 1,500,000 units daily for cure.[66, 67]

Vitamin E. The essentiality of vitamin E in human nutrition has not been established as yet. Although specific manifestations of vitamin E deficiency have been demonstrated in animals, no similar deficiency syndrome in man is known. Likewise, the human requirement, if there is one, has not been determined. Several series of measurements of the blood plasma level of vitamin E in normal human subjects show a range of 0.39 to 2.02 mg. per 100 cc.[68-70] Much lower plasma levels of vitamin E have been found in persons with malnutrition, sprue and impaired fat absorption.[68, 70] The significance of decreased levels of vitamin E in the plasma is not known.

Vitamin K. The minimal requirement for vitamin K is 1 mg. per day or less. The quantity needed is usually supplied in sufficient amounts by the diet and by intestinal synthesis.[44, 51] To prevent hemorrhagic manifestations in the newborn, it is advisable to give supplements of vitamin K to the mother during the last month of pregnancy.[44] When prothrombin deficiency occurs, as in cases of impaired intestinal absorption, 2 mg. of vitamin K per day is more than enough to restore the prothrombin level to normal.[71]

Recommended Dietary Allowances

The National Research Council constantly reviews data derived from investigations into nutritional requirements, such as those surveyed above, and publishes revisions of recommendations for dietary allowances from time to time. In keeping with advancing knowledge about minimal requirements for vitamins, it is interesting to note the

downward trend of recommendations in the latest 1948 National Research Council revision.[51] The specific vitamin allowance recommendations for those vitamins for which definite deficiency states have been recognized are summarized as follows:

Vitamin A — 5000 I.U. per day; 8000 I.U. per day during lactation.

Thiamine — 1.0 mg. per day for sedentary persons to 1.8 mg. per day for those doing heavy labor.

Riboflavin — 1.5 to 1.8 mg. per day; 3.0 mg. per day during lactation.

Niacin — 12 mg. per day for sedentary life to 18 mg. per day for heavy labor.

Vitamin C — 70 to 75 mg. per day; 150 mg. per day during lactation.

Vitamin D — 400 I.U. per day during childhood, adolescence, pregnancy and lactation; minimal amounts for adults generally.

Vitamin K and folic acid are recognized, but no quantitative recommendations are made.

The report points out that food supplying adequate thiamine, riboflavin and niacin will inherently supply sufficient quantities of the remaining components of the vitamin B complex.[51] In my opinion, this statement constitutes a strong argument for utilizing food to combat deficiency states and for eliminating the use of crystalline, synthetic or purified vitamin supplements, which cannot contain all nutrients in balanced quantities.

In discussing these recommended dietary allowances, Jeans[44] emphasizes that they are not in any way a yardstick of requirements, but are definitely above average requirements, sometimes reaching twice the minimum. The allowances are a goal for ensuring good general nutrition, but "persons ingesting less than the allowances are not deficient *ipso facto*."[44]

It is my opinion that many claims that the American diet is inadequate are based upon use of the National Research Council's recommended dietary allowance, as if the levels appearing there were minimal requirements rather than above average. Jeans believes that the over-all American dietary intake is much more sufficient in the vitamins than is often stated.

Such a lengthy review of recent data about minimal requirements seems justified because they are the foundation for evaluating the adequacy of diets. If food intake does not supply the minimal requirement of essential vitamins, supplements are justified. If, on the other hand, dietary intakes meet the minimal requirements, supplements are of little value, unless they cause an improvement in health and well-being beyond that resulting from an unsupplemented diet. These two alternatives will be examined in the next section of this review.

(*To be continued*)

References

1. High potency vitamin sales increase 91%. *Drug Topics Red Book*. 574 pp. New York: Topics Publishing Co., Inc., 1948-49. P. 8.
2. Ingelfinger, F. J. Parenteral use of vitamin preparations. *New Eng. J. Med.* **233**:379-385 and 409-417, 1945.
3. Cowgill, G. R. Recent advances in knowledge of vitamins. *J. Mt. Sinai Hosp.* **14**:80-97, 1947.
4. Harris, L. J. All the vitamins. *Brit. M. J.* **2**:681-684, 1947.
5. Elvehjem, C. A. Vitamin B complex. *J. A. M. A.* **138**:960-971, 1948.
6. Gripwall, E. Vitamin B complex: its importance and therapeutic value in internal medicine. *Acta med. Scandinav.* (Supp. 213): 171-179, 1948.
7. Embree, N. Recent advances in chemistry and nutrition of fat soluble vitamins. *Oil and Soap* **23**:305-307, 1946.
8. Sargent, F., II. "Folic acid": pteroylglutamic acid and related substances. *New Eng. J. Med.* **237**:667-672 and 703-707, 1947.
9. Wright, L. D. Significance of anti-vitamins in nutrition. *J. Am. Diet. A.* **23**:289-298, 1947.
10. Pett, L. B. Use and abuse of vitamins. *Canad. M. A. J.* **52**:488-491, 1945.
11. Alexander, B., and Landwehr, G. Studies of thiamine metabolism in man. I. Thiamine balance. Normal requirement of vitamin B_1 and role of fecal thiamine in human nutrition. *J. Clin. Investigation* **25**:287-293, 1946.
12. Cayer, D. Recognition and treatment of early vitamin deficiency states. *J. A. M. A.* **132**:558-561, 1946.
13. Robertson, E. C., and Morgan, A. L. Effects of added vitamin A on conjunctiva and level of vitamin A in blood. *J. Nutrition* **31**: 471-484, 1946.
14. Keys, A., Henschel, A., Taylor, H. L., Mickelsen, O., and Brozek, J. Experimental studies on man with restricted intake of B vitamins. *Am. J. Physiol.* **144**:5-42, 1945.
15. Berryman, G. H., et al. Some factors influencing biochemical appraisal of group nutritional status. *Am. J. Physiol.* **145**:625-631, 1946.
16. Berryman, G. H., and Henderson, C. R. Further observations on factors influencing biochemical appraisal of nutritional status. *Am. J. Physiol.* **149**:142-148, 1947.
17. Cayer, D., and Cody, S. Urinary excretion of niacin and riboflavin in patients with acute infections and various chronic diseases. *Am. J. M. Sc.* **215**:273-277, 1948.
18. Gardner, J., Parsons, H. T., and Peterson, W. H. Human utilization of biotin from various diets. *Am. J. M. Sc.* **211**:198-204, 1946.
19. Sharp, E. A., and vonder Heide, E. C. Utilization of vitamin B_{12} conjugate in pernicious anemia. *Am. J. Clin. Path.* **17**:761-769, 1947.
20. Oldham, H. G., Davis, M. V., and Roberts, L. J. Thiamine excretions and blood levels of young women on diets containing varying levels of B vitamins, with some observations on niacin and pantothenic acid. *J. Nutrition* **32**:163-180, 1946.
21. Harris, A. D., and Moore, T. Vitamin A in infective hepatitis. *Brit. M. J.* **1**:553-559, 1947.
22. Hartzler, E. Vitamin A content of human blood plasma as index of carotene utilization. *J. Nutrition* **36**:381-390, 1948.
23. Callison, E. C., and Orent-Keiles, E. Availability of carotene from carrots and further observations on human requirements for vitamin A and carotene. *J. Nutrition* **34**:153-165, 1947.
24. Smith, D. A. Nutritional neuropathies in civilian internment camp Hong Kong, January, 1942–August, 1945. *Brain* **69**:209-222, 1946.
25. Salcedo, J., Jr., Carrasco, E. O., Jose, F. R., and Valenzuela, R. C. Studies on beriberi in endemic sub-tropical area. *J. Nutrition* **36**: 561-577, 1948.
26. Foltz, E. E., Barborka, C. J., and Ivy, A. C. Level of vitamin B-complex in diet at which detectable symptoms of deficiency occur in man. *Gastroenterology* **2**:323-344, 1944.
27. Berryman, G. H., et al. Effects in young men consuming restricted quantities of B-complex vitamins and protein, and changes associated with supplementation. *Am. J. Physiol.* **148**:618-647, 1947.
28. Hathaway, M. L., and Strom, J. E. Comparison of thiamine synthesis and excretion in human subjects on synthetic and natural diets. *J. Nutrition* **32**:1-8, 1946.
29. Tuttle, W. W., Wilson, M., Daum, K., and Rhodes, H. Influence of various levels of thiamine intake on physiological response. III. Reaction time. *J. Am. Diet. A.* **25**:21-27, 1949.
30. Holt, L. E., Jr., et al. Thiamine requirement of normal infant. *J. Nutrition* **37**:53-66, 1949.
31. Horwitt, M. K., and Kreisler, O. Determination of early thiamine-deficient states by estimation of blood lactic and pyruvic acids after glucose administration and exercise. *J. Nutrition* **37**:411-427, 1949.
32. Butler, R. E., and Sarett, H. P. Effect of isocaloric substitution of alcohol for dietary carbohydrate upon excretion of B vitamins in man. *J. Nutrition* **35**:539-548, 1948.
33. Alleman, R. J., and Stollerman, G. H. Course of beriberi heart disease in American prisoners-of-war in Japan. *Ann. Int. Med.* **28**: 949-962, 1948.
34. Rafsky, H. A., Newman, B., and Jolliffe, N. Relationship of gastric acidity to thiamine excretion in aged. *J. Lab. & Clin. Med.* **33**: 118-123, 1947.
35. Garber, M., Marquette, M. M., and Parsons, H. T. Availability of vitamins from yeasts. V. Differences in influence of live yeast on absorption of pure thiamine hydrochloride, pure riboflavin and nitrogen by human subjects, and effect of distribution of vitamin doses. *J. Nutrition* **38**:225-236, 1949.

36. Lund, C. C., et al. Ascorbic acid, thiamine, riboflavin and nicotinic acid in relation to acute burns in man. *Arch. Surg.* **55**:557-583, 1947.

37. Levenson, S. M., et al. Ascorbic acid, riboflavin, thiamin, and nicotinic acid in relation to severe injury, hemorrhage, and infection in human. *Ann. Surg.* **124**:840-856, 1946.

38. Culver, P. J. Cited by Means, J. H. *The Thyroid and Its Diseases.* Second edition. 571 pp. Philadelphia: J. B. Lippincott Co., 1948. Pp. 53-55 and 400-402.

39. Davis, M. V., Oldham, H. G., and Roberts, L. J. Riboflavin excretions of young women on diets containing various levels of B vitamins. *J. Nutrition* **32**:143-161, 1946.

40. Oldham, H., Lounds, E., and Porter, T. Riboflavin excretions and test dose returns of young women during periods of positive and negative nitrogen balance. *J. Nutrition* **34**:69-79, 1947.

41. Andreae, W. A., Schenker, V., and Browne, J. S. L. Riboflavin metabolism after trauma and during convalescence in man. *Federation Proc.* **5**:3, 1946.

42. Hathaway, M. L., and Lobb, D. E. Comparison of riboflavin synthesis and excretion in human subjects on synthetic and natural diets. *J. Nutrition* **32**:9-18, 1946.

43. Brewer, W. D., Porter, T., Ingalls, R., and Ohlson, M. A. Urinary excretion of riboflavin by college women. *J. Nutrition* **32**:583-596, 1946.

44. Jeans, P. C. Recent revisions in recommended dietary allowances. *J. Am. Diet. A.* **25**:13-17, 1949.

45. Krehl, W. A., Elvehjem, C. A., and Hart, E. B. Comparative value of niacin and nicotinamide. *Nutrition Rev.* **4**:65-67, 1946.

46. Krehl, W. A., Teply, L. J., Sarma, P. S., and Elvehjem, C. A. Growth-retarding effect of corn in nicotinic acid-low rations and its counteraction by tryptophane. *Science* **101**:489, 1945.

47. Woolley, D. W. Occurrence of "pellagragenic" agent in corn. *J. Biol. Chem.* **163**:773, 1946.

48. Hawkins, W. W., and Barsky, J. Experiment on human vitamin B_6 deprivation. *Science* **108**:284-286, 1948.

49. Glusman, M. Syndrome of "burning feet" (nutritional melalgia) as manifestation of nutritional deficiency. *Am. J. Med.* **3**:211-223, 1947.

50. West, R. Activity of vitamin B_{12} in Addisonian pernicious anemia. *Science* **107**:398, 1948.

51. National Research Council. Food and Nutrition Board. *Recommended Dietary Allowances.* Revised. Reprint and Circular Series No. 129, 1948. Washington, D. C.

52. Vitamin C requirement of human adults: experimental study of vitamin C deprivation in man. Preliminary report by Vitamin C Subcommittee of Accessory Food Factors Committee, Medical Research Council. *Lancet* **1**:853-858, 1948.

53. Haines, J. E., Klosterman, A. M., Hauck, H. M., Delaney, M. A., and Kline, A. B. Tissue reserves of ascorbic acid in normal adults on three levels of intake. *J. Nutrition* **33**:479-489, 1947.

54. Johnstone, W. M., Drake, T. G. H., Tisdall, F. F., and Harvie, F. H. Study of ascorbic acid metabolism of healthy young Canadians. *Canad. M. A. J.* **55**:581-585, 1946.

55. Dodds, M. L., and MacLeod, F. L. Blood plasma ascorbic acid levels on controlled intakes of ascorbic acid. *Science* **106**:67, 1947.

56. Report by Technical Commission on Nutrition on work of third session. *Bull. Health Organ., League of Nations* **7**:475, 1938.

57. Crandon, J. H., Lund, C. C., and Dill, D. B. Experimental human scurvy. *New Eng. J. Med.* **223**:353-369, 1940.

58. Slobody, L. B., Benson, R. A., and Mestern, J. Induction of vitamin C subnutrition: comparison of intradermal tests with plasma ascorbic acid levels. *J. Pediat.* **28**:134-139, 1946.

59. Lowry, O. H., Bessey, O. A., Brock, M. J., and Lopez, J. A. Interrelationship of dietary, serum, white blood cell, and total body ascorbic acid. *J. Biol. Chem.* **166**:111-119, 1946.

60. Durham, M. P., Francis, G. E., and Wormall, A. Further observations on vitamin-C survey of medical students. *Lancet* **2**:936-940, 1946.

61. Wolfer, J. A., Farmer, C. J., Carroll, W. W., and Manshardt, D. O. Experimental study in wound healing in vitamin C depleted human subjects. *Surg., Gynec. & Obst.* **84**:1-15, 1947.

62. Bartlett, M. K., Jones, C. M., and Ryan, A. E. Vitamin C studies on surgical patients. *Ann. Surg.* **111**:1-26, 1940.

63. *Idem.* Vitamin C and wound healing. *New Eng. J. Med.* **226**:469-481, 1942.

64. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., and Roos, A. Osteomalacia and late rickets: various etiologies met in United States with emphasis on that resulting from specific form of renal acidosis, therapeutic indications for each etiological subgroup and relationship between osteomalacia and Milkman's syndrome. *Medicine* **25**:399-479, 1946.

65. Fourman, L. P. R., and Spray, G. H. Absorption of vitamin D in steatorrhoea. *Brit. M. J.* **1**:142-144, 1948.

66. Albright, F., Butler, A. M., and Bloomberg, E. Rickets resistant to vitamin D therapy. *Am. J. Dis. Child.* **54**:529-547, 1937.

67. McCance, R. A. Osteomalacia with Looser's nodes (Milkman's syndrome) due to raised resistance to vitamin D acquired about age of 15 years. *Quart. J. Med.* **16**:33-46, 1947.

68. Harris, P. L., Hickman, K. C. D., Jensen, J. L., and Spies, T. D. Survey of blood plasma levels of vitamin A, carotene, ascorbic acid, and tocopherols of persons in area of endemic malnutrition. *Am. J. Pub. Health* **36**:155-160, 1946.

69. Steinberg, C. L. Treatment of Dupuytren's contracture, form of fibrositis. *S. Clin. North America* **30**:221-231, 1946.

70. Darby, W. J., Cherrington, M. E., and Ruffin, J. M. Plasma tocopherol levels in sprue. *Proc. Soc. Exper. Biol. & Med.* **63**:310-312, 1946.

71. Bercovitz, Z., and Page, R. C. Metabolic and vitamin studies in chronic ulcerative colitis. *Ann. Int. Med.* **20**:239-254, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35501

PRESENTATION OF CASE

A seventy-year-old man was brought to the Emergency Ward in shock by the Fire Department.

He was feeling relatively well until one and a half hours prior to entry, when he suddenly collapsed while waiting in the office of his physiotherapist. A physician found the patient cold and clammy and sweating profusely without obtainable pulse or blood pressure. Oxygen was given, and tourniquets were applied to the legs. Soon afterward he regained consciousness and stated that no pain preceded this episode.

Twelve years prior to admission he had a cerebrovascular accident from which a mild left hemiparesis remained and since that time his blood pressure averaged 220 systolic, 140 diastolic. Seven years before entry he suffered a myocardial infarction and was treated at a community hospital. His recovery was complete as confirmed by an electrocardiogram made six months before entry. This showed normal rhythm at a rate of 70, left-axis deviation, normal PR and QRS intervals, small upright T waves in the limb leads and upright T waves in the precordial leads. For the past twelve years he had led a quiet life and at no time complained of symptoms of congestive failure or hypertension. One month prior to entry he developed a generalized muscular achiness that was somewhat improved by physiotherapy.

Physical examination revealed a very pale, cold, sweaty, moderately obese man in profound shock but not unconscious. There was no cyanosis of the face or distention of the neck veins. The pupils were constricted but reactive. The lungs were clear except for a few moist basal rales. The heart was not grossly enlarged, and the sounds were barely audible but regular. There was no gallop and no murmurs. The abdomen was prominent, soft and hyperresonant in the left upper quadrant. There was moderate tenderness beneath the left costal margin and a firm fullness over the descending colon, but no obvious masses were felt. There was no ankle edema. The legs were cold, pale and pulseless.

Neurologic examination showed a slightly increased muscular tone of the left arm over the right, and the spontaneous arm movements were easier on the right than the left. The reflexes were not remarkable except for a decreased response of the left knee jerk.

The temperature was 99°F., the pulse 90, and the respirations 22. The blood pressure was 95 systolic, 75 diastolic.

Urinalysis revealed no abnormalities except for a +++ test for albumin. Examination of the blood disclosed a white-cell count of 28,700, with 82 per cent neutrophils, 15 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The hemoglobin was 11.5 gm. per 100 cc. (three weeks prior to this determination it was 14 gm.). The nonprotein nitrogen was 49 mg. per 100 cc. and the prothrombin time was 15 seconds (normal, 15 seconds). An electrocardiogram showed sinus tachycardia at a rate of 110 with a PR interval of 0.17 second and a QRS interval of 0.08 second. There were prominent Q waves in Lead 2, 3, and AVF. The T waves were flat in Lead 2 and V_6, inverted in Lead 3 and AVF and upright in the other leads. Another electrocardiogram taken on the second hospital day disclosed normal rhythm at a rate of 95 to 100 with moderate left-axis deviation, inverted T wave in Lead 1 (for the most part late), flat T wave in Lead 2, and slightly elevated ST segment and deep Q_2 wave in AVF. The precordial leads showed low T waves with slightly late notched TV_4, and late inversion of the T wave in V_6.

Shortly after admission the patient improved. The blood pressure rose to 110 systolic, 95 diastolic, and the pulse became more firm; however, he remained in shock. Because of persistence of collapse four hours later a slow blood transfusion was administered, after which he became rested and slept quietly. On the second hospital day the patient awoke lucid, appearing dramatically improved, but the blood pressure remained low—100 systolic, 80 diastolic. The hemoglobin had decreased to 9 gm., and the white-cell count to 19,800. He complained of aches all over when moving and mentioned that his "bowels hurt."

On the third hospital day he was restless and disoriented, and he suddenly began to breathe heavily and went into shock; the blood pressure and pulse became unobtainable, and shortly thereafter he died.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT S. PALMER*: When a person faints, one cannot say right off whether or not it is benign

*Associate physician, Massachusetts General Hospital.

fainting. When fainting occurs in an elderly man whose subsequent course excludes fainting of the benign or transient sort, many people think of myocardial infarct, and so do I. In elderly persons particularly myocardial infarction may be without pain and may be heralded by syncope. Although it is unusual, sudden collapse may happen at the onset in cerebral hemorrhage, and also may be caused by overwhelming infection, an acute condition of the abdomen, or internal hemorrhage. This man's blood pressure was not the ordinary wide-pulse-pressure type seen in hypertension of the elderly, which we think is due to large-vessel sclerosis. The diastolic pressure was elevated and may have been due to chronic vascular nephritis. I have here the electrocardiogram taken seven years before entry, a feature of which is a high ST segment in Lead 3, with late inversion and elevated ST segment in Lead 2. If the clinical course were characteristic I should think we might accept the given diagnosis of posterior myocardial infarction at that time. Recovery seemingly was satisfactory, and an electrocardiogram made six months before entry had returned to normal in respect to T-wave changes. Coming back to the conditions that can cause shock, I wonder about an acute condition of the abdomen and hemorrhage. From the physical signs given here, I can see nothing that really helps me definitely to rule abdominal disease in or out. When a patient is in profound shock, of course, the signs of an acute condition of the abdomen are equivocal.

The neurologic examination suggests the residua of an old cerebral thrombosis. In summary, the background of this patient, admitted in profound shock, is one of arterial hypertension with diffuse vascular disease: cerebral, cardiac and renal.

Do the laboratory data help to settle the differential diagnosis of shock due to myocardial infarction, overwhelming infection, acute abdomen or hemorrhage? The white-cell count of 28,700 was high for shock and for hemorrhage; it was not too high for an overwhelming infection. It was rather high for myocardial infarction. The hemoglobin was definitely lower than three weeks earlier. Could he have lost 2.5 gm. of hemoglobin from shock alone, or was it an indication of hemorrhage and shock in a person who had lost enough blood so that he did not concentrate since ordinarily in a shock state one expects hemoconcentration? The nonprotein nitrogen of 49 mg. per 100 cc., perhaps slightly elevated, may have been a manifestation of shock, although it possibly was related to chronic vascular nephritis. The admission electrocardiogram, which I have here, is the usual complete tracing and should help us.

In Lead 3 there is a suggestion of elevated ST segment and definite late inversion of the T wave, and in the precordial lead there is low QRS voltage and a low T wave. Previously we did not have unipolar limb leads nor a precordial lead in the sixth position, but we know from the previous electrocardiogram at least that the T wave in the conventional third lead was low upright, whereas it was inverted on this one later tracing. This would be consistent with the expected change of a posterior myocardial infarction. The second tracing, taken on the next day, showed in addition a rather depressed ST segment in Lead 1 and late inversion of the T wave. In Lead 3 the T wave is now upright, which is disturbing if we are thinking of posterior or basal infarction. There are slight changes in the unipolar limb leads, which may be seen in posterior or basal infarction. The sixth precordial lead shows an additional change. There is quite good QRS voltage, with late inversion of the T wave. It is far enough out so that it may be close to but not directly over an area of infarction at the base of the left ventricle.

Regarding progress while the patient was in the hospital, blood was given. Transfusion is good therapy for shock and not infrequently may be indicated in the shock of myocardial infarction. The hemoglobin was still lower on the second hospital day. If we can trust the laboratory determinations, this patient had lost about a third of his hemoglobin. The white-cell count was now 19,800. I do not know what the "aches all over" represented and whether or not they were connected with the same complaint of a month prior to admission. I find nothing specific enough in the statement that his "bowels hurt" to help me.

This elderly man with hypertension and cerebral, cardiac and renal sclerosis had suffered an old posterior or basal myocardial infarction and a cerebral thrombosis with a left hemiparesis. When a person is found in shock, and the shock persists, there is no way of telling from the signs whether or not shock was due to a heart condition, an acute overwhelming infection, rupture of a hollow viscus or hemorrhage. The appearance and indeed the symptoms of these different conditions sometimes cannot be told apart. He may have had another attack of coronary thrombosis, and if so, from the diffuse changes in the electrocardiogram, it must have been a large one. Could he have had an acute condition of the abdomen? There was no sign of peritoneal irritation and nothing to indicate ileus, and there was nothing in the past history to suggest ulcer or gall-bladder disease or anything that would make us think that he had a rupture of a hollow viscus. Did he have internal hemorrhage? I have been fooled by an elderly person who I thought was having a mild attack of coronary insufficiency, and subsequently was proved to have had hemorrhage into, of all things, a hepatoma, which was quite large. Did this patient bleed into the gastrointestinal tract? In my experience a person of middle age or older who has a known ulcer and who is known to be bleeding and dies in uncontrollable

shock sometimes proves to have had a silent myocardial infarction. If this patient had gastrointestinal bleeding we should have seen or heard of blood at one end or the other of his intestinal tract. It is still conceivable that he may have bled somewhere, which is not apparent to me from the data at hand.

Let us see where we stand. Did he have a coronary thrombosis? Somewhat against this diagnosis is the syncope but it is not too unusual, especially in an elderly man. He did not have pain. At least when he became conscious he said that he had no pain. Again this is unusual but does not exclude the diagnosis. He had a very high white-cell count—higher than in most cases of myocardial infarction, let us say. The electrocardiographic picture is not complete enough for me to be actually sure of a diagnosis, perhaps because he did not live long enough to develop the complete pattern. Perhaps the exploring electrodes were near but not directly over dead muscle. Did he have hemorrhage? The high white-cell count and the loss of one third of his hemoglobin are in favor of hemorrhage. A hematocrit and other blood studies would have helped since I do not like to depend on the hemoglobin determinations alone. Since we have nothing to point to an acute overwhelming infection or peritonitis and since we do not know where he bled, I am inclined to discard these possibilities and to suggest that he had extensive myocardial infarction, posterolateral or posterior, perhaps involving the septum extensively.

Dr. Bernard Jacobson: When he entered the Emergency Ward, examination revealed nothing in the rectum, and the small bit of stool that was obtained was brown and guaiac negative.

Dr. Palmer: That is evidence against hemorrhage into the gastrointestinal tract. What would happen if a person ruptured the ventricular septum, I do not know. Did he die of ventricular fibrillation? If he had extensive old myocardial disease and an additional fresh infarction he may have had ventricular fibrillation, and no specific immediate cause for death was found. Finally, did he have overwhelming pulmonary embolism? He was an old man, who had been in bed three days in profound shock, not moving very much, and he had had tourniquets on all four extremities. I think he may have had a pulmonary embolism as a final episode.

A Physician: If this were a gastrointestinal hemorrhage, could the shock produce changes that would be consistent with these electrocardiograms?

Dr. Palmer: It's a wonderful suggestion. If he was anemic and his hematocrit was low he would have very few red cells circulating. That might cause myocardial ischemia and alteration in the electrocardiogram. I do not know, but I suppose it could cause such electrocardiographic changes and therefore might be misleading. I think that is a good point.

Dr. Samuel Goldfarb: Do you suppose the hemoglobin levels are correct? This man had a hemoglobin of 14 gm. before his accident and 11.5 gm. on admission, going down to 9 gm. the next day, without taking into consideration that he probably received 500 cc. of blood. How often do we see myocardial infarction produce rapid and sudden loss of hemoglobin?

Dr. Palmer: I do not know whether it could happen. I think hemoglobin values alone are doubtful but since the hemoglobin went from 14 gm. to 11 gm. and then down to 9 gm. it almost makes me think something like that has happened.

A Physician: Could aneurysm rupturing the septum occur without pain?

Dr. Palmer: I suppose it could, though I do not know.

Dr. Jacobson: There is a slight correction to the record. I saw the patient at a physiotherapist's office downtown and found him completely unconscious in profound collapse, and I want to pay tribute to the Fire Department of the City of Boston for the prompt arrival of oxygen in one minute flat. I transferred him here as soon as possible. The statement is made that as soon as he regained consciousness he said he had no pain. He was unconscious when I saw him at quarter to two in the afternoon and he remained unconscious until seven o'clock the following morning. Thereafter he complained of slight tenderness on palpation of the left lower abdomen.

A Physician: It was mentioned that the pulsations in the legs were absent on one examination. Did that come back or remain absent?

Dr. Jacobson: The dorsalis pedis and posterior tibial pulsations had been absent for the past year or more.

Dr. Goldfarb: Is this history compatible with dissecting aneurysm?

Dr. Palmer: I suppose dissecting aneurysm could occur without pain. I have known of one patient, a man in the Home for Aged Men with no history of pain, but when he died of something else, the evidence of former dissection was found.

Dr. Jacobson: Dr. Bland saw the patient on entry to the hospital. We were worried about the 11.5 gm. of hemoglobin in a patient with hemoconcentration of shock. During the following fourteen hours we were considerably worried by the fact that the left abdomen seemed a little tense and the patient winced when we touched it. On the following day when he was conscious his left abdomen was still a little tender but not spastic. No masses were felt. I also might add that he began to urinate eight or nine hours after he entered the hospital and that the urinary output thereafter was adequate.

Dr. Palmer: That would go with shock.

Clinical Diagnoses

Arteriosclerotic heart disease.
Infarction of myocardium, due to arteriosclerotic coronary thrombosis.

Dr. Palmer's Diagnoses

Myocardial infarction, extensive, recent.
Old posterior myocardial infarction.
Hypertension, with diffuse vascular sclerosis.
Old cerebral thrombosis.

Anatomical Diagnoses

Arteriosclerosis, generalized, with ruptured arteriosclerotic aneurysm of abdominal aorta.
Retroperitoneal hematoma, massive.
Infarct of heart, old.
Infarct of cerebellum, old.
Hypertrophy of heart.
Nephrosclerosis.

Figure 1.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy showed that the falling hemoglobin was the key to this case. We found on opening the peritoneal cavity that the retroperitoneal tissues on the left side of the abdomen way down into the pelvis were filled with clotted blood. This was the result of rupture of a saccular arteriosclerotic aneurysm of the aorta, which lay just above the bifurcation (Fig. 1). The clot showed evidence of layering, and I think he must have had several episodes of bleeding at various times. The other findings were merely those of long-standing hypertensive heart disease and severe arteriosclerosis: shrunken kidneys, hypertrophied heart with an old completely healed posterior infarct and marked atheroma of the vessels of the circle of Willis, with a small area of softening of the cerebellum. The extraordinary thing about the story is the lack of obvious pain. Dissection of large amounts of blood through the retroperitoneal tissues in my experience almost always has been associated with the most intense pain. Probably his mental clouding had a good deal to do with the fact that he did not complain of this.

Case 35502

Presentation of Case

A sixty-nine-year-old widow entered the hospital because of extreme weakness for about one year and jaundice for about one month.

The patient dated the onset of poor health from an operation for ruptured appendix followed by peritonitis and drainage at the age of thirty-five. A postoperative ventral hernia was repaired but recurred. At the age of forty-four she received the diagnosis of "pernicious anemia" while seeing a doctor for reasons she did not remember. For this she was urged to eat raw liver, which she was unable to do because of vomiting; injections were discontinued because they were painful; "copper and iron" tablets were taken. She had not had antianemia treatment for years. A subtotal thyroidectomy was performed at the age of sixty-three for "toxic goiter." Radiograms at another hospital at the age of sixty-seven showed an enlarged heart; an electrocardiogram disclosed auricular fibrillation, left bundle-branch block and left ventricular strain. Although she had not considered herself in good health for "many" years, the patient noticed that her usual weakness became more pronounced six months before entry, following the death of a son; anorexia likewise appeared and increased. During this time her weight had decreased from 178 to 158 pounds (several years previously she had weighed 240 pounds but had not tried to reduce). During the four weeks before entry her attention had been called to the gradually increasing yellowish discoloration of her skin, which had steadily progressed. Itching of the skin over the arms and anterior chest was present during the first week of jaundice but then abated. This was not accompanied by pain, clay-colored stools, nausea, vomiting or fever.

The urine was noted to be darker than usual. There was no previous episode of jaundice, no change in bowel habits or stools and no history of exposure to jaundiced persons, chemicals or transfusions. She did not drink alcohol.

Physical examination revealed a moderately icteric woman, lying in bed in moderate distress as evidenced by rapid, forced respirations. Moderate palmar erythema was noted. No spider angiomas were present. The scleras were icteric. The chest was emphysematous; moist rales were present at both bases, more marked on the left. The heart was enlarged, the point of maximal impulse being 2 cm. left of the midclavicular line. The rhythm was irregular. The sounds were of good quality; the pulmonic second sound was markedly greater than the aortic; a Grade II, rough systolic murmur was best heard at the lower sternal border. The abdomen was obese. A large ventral hernia occupied the left lower quadrant. The liver was palpated 11 cm. below the costal margin in the midclavicular line; the edge was firm, sharp and nontender. The splenic tip was questionably palpable. A ++ pitting edema was present over the lower two thirds of the leg and the sacrum. The knee jerks and ankle jerks were absent; vibratory sense was absent in both ankles and the right knee.

The blood pressure was 92 systolic, 48 diastolic. The temperature was 100°F., the pulse 96, and the respirations 28.

The blood showed a red-cell count of 3,820,000, with a hemoglobin of 10.8 gm. The white-cell count, was 7600, with 88 per cent neutrophils, and later ranged between 12,000 and 16,000. Urinalysis revealed a + test for albumin, and bile. The fasting blood sugar was 124 mg. per 100 cc., the sodium 133.9 milliequiv., and the chloride 101 milliequiv. per liter. The total protein was 5.6 gm. per 100 cc., with an albumin-globulin ratio of 3.3/2.33. The nonprotein nitrogen was 20 mg. per 100 cc., and the alkaline phosphatase 12.9 units, reaching 22.3 units on the eighteenth day. The prothrombin time was normal on admission and only slightly elevated later. The van den Bergh reaction was 8.7 mg. per 100 cc. direct, 13.2 mg. indirect. The amylase was 33 units per 100 cc.; the cephalin-flocculation test was + in twenty-four hours, ++ in forty-eight hours and, twenty days later, +++ in twenty-four hours and ++++ in forty-eight hours. The cholesterol was 139 mg. and the cholesterol esters 54 mg. per 100 cc.; the thymol flocculation was negative, the thymol turbidity 2.10 units, the urine urobilinogen 3.0 to 7.3 Ehrlich units, and the stool urobilinogen normal. The stools were guaiac negative, and cultures were negative for pathogens. A heterophil-antibody test was negative. The blood culture was negative. The clotting time (without tube) was 9 minutes, and the bleeding time (ear puncture), 1 minute. A bone-marrow aspiration revealed a slight shift to the left in the myeloid and also in the erythroid series; no megaloblasts or other abnormal cells were seen. An electrocardiogram revealed auricular fibrillation, at a rate of 100, a QRS complex of 0.12 second, low to absent R wave in Lead V_4 and V_6 and left bundle-branch block. A gastric aspiration on the fifth hospital day failed to reveal any free acid, but "pure bile" was present.

Radiographic studies showed left ventricular and left auricular enlargement. The aorta was tortuous and calcified. The right leaf of the diaphragm was elevated but on fluoroscopic examination moved as well as the left. Hepatomegaly and splenomegaly were prominent features. A barium enema was unsatisfactory because of the patient's inability to retain sufficient barium; however, diverticula were demonstrated in the sigmoid region, and the cecum was high-placed. A gastrointestinal series revealed no esophageal varices. A small hiatus hernia was present. No intrinsic abnormality of the stomach, duodenal bulb or duodenal loop was present. The duodenal loop was not enlarged. A small-bowel series was not remarkable, except for one segment of atonic bowel on the three-hour film. It was also noted that the bones were atrophic with fairly marked degenerative changes.

A sigmoidoscope was passed to 13 cm., with great difficulty. The bowel was very spastic and was intensely hyperemic.

The temperature remained elevated in irregular fashion, reaching 104°F. on the first, sixth and seventh hospital days, dropping to 99°F. and below on the eighth and ninth days, and becoming elevated again, gradually reaching 104°F. on the fourteenth day, normal on the fifteenth day and up to 104°F. again on the twenty-second and twenty-third days. Although the patient was reluctant to take food and refused to force fluids, she was kept well hydrated, and the caloric intake increased by frequent prompting. It was noted on one occasion that appetite increased, and the patient was subjectively better coincident with a high rise in temperature. Therapeutic measures consisted mainly of Digitoxin, 0.15 mg. daily, Crysticillin, 300,000 units daily, Hykinone, 4.8 mg. daily, and dihydrostreptomycin, 1.0 gm. daily, as well as supportive and antipyretic measures. Mercuhydrin was given on occasion. The patient's general condition grew steadily worse. On the fifteenth hospital day abdominal distention had become an increasingly prominent feature, being only somewhat relieved by enemas and stupes.

A liver biopsy on the twenty-first day was reported as follows:

> The portal areas show increase in the number of small-bile ducts and a moderately severe inflammatory reaction in which polymorphonuclears are numerous. Small cholangioles are dilated, and there are foci of pseudotubular change in the liver cords. Two foci of necrosis and degeneration of liver cells are seen. No inspissation of bile in the cholangioles or canaliculi is seen, and there is no bile pigmentation in the liver cells. The findings nevertheless suggest obstruction in the extrahepatic biliary tract.

On the twenty-fifth day it was noted that the jaundice had deepened, and the liver edge was only 4 cm. below the costal margin. Stupor increased, and the patient died quietly, without change in the vital signs, on the twenty-sixth hospital day.

Differential Diagnosis

Dr. Alfred L. Duncombe*: May we see the x-ray films?

Dr. Stanley M. Wyman: The film of the chest taken in the upright position shows the heart to be considerably enlarged to the left, probably in the region of the left ventricle. The tortuous, calcified aorta is well seen, and also the elevation of the right leaf of the diaphragm. This appears to be rather localized anteriorly and probably represents localized enlargement of the liver in this region. The spleen is greatly enlarged, extending down to the crest of the ilium, and there are a number of round calcific shadows overlying the spleen suggesting phleboliths in the spleen itself.

The kidney shadows are not adequately seen on any film, but they may be small. One film of the attempted barium enema shows nothing remarkable except for diverticula in the sigmoid. The films from the gastrointestinal series show some pressure on the lesser-curvature aspect of the stomach, with depression of the duodenal bulb downward. This is well seen in the spot film. The esophagus itself is quite well demonstrated, and there is no evidence of varices. There is no evidence of pressure on the second portion of the duodenum in its medial aspect. The stasis in the small bowel, I think, may be accounted for by the patient's large hernia, which is seen at this point.

Dr. Duncombe: Will you comment on the barium swallow?

Dr. Wyman: It outlines an essentially normal esophagus, which is pushed backward by the enlarged heart.

Dr. Duncombe: The problem is that of a woman with painless jaundice of a number of weeks' duration, following a period of increasing poor health, which went on to a rather rapidly fatal termination.

There are several things in the past history that should be mentioned and disposed of. The diagnosis of pernicious anemia was made twenty-five years before admission — incidentally, that was two years ahead of the publication of Dr. Minot's paper. Perhaps it is an error in the history. She probably did not have pernicious anemia at any time. Her blood picture was not that of pernicious anemia and the bone-marrow biopsy did not show the findings of pernicious anemia. She had a toxic goiter removed six years previously, with weight loss of some 50 or 60 pounds since that time. The possibility of recurrent thyrotoxicosis should be considered, but there is no other evidence for it.

Then she was known to have had heart disease of some type for a few years. The heart was enlarged chiefly in the region of the left ventricle. She was fibrillating. There was no history of hypertension. Her blood pressure in the hospital was low — 92 systolic, 48 diastolic. The electrocardiogram is of no value in the diagnosis of the heart disease but confirms the presence of fibrillation. She had a relatively loud systolic murmur heard best at the lower border of the sternum. This murmur is consistent with disease of the aortic valve in a person who has developed failure and a fall in blood pressure and is acutely ill. I think it most likely that the autopsy showed disease of the aortic valve and a large left ventricle.

Is it possible that the heart disease was a major factor in her present hospital admission? It seems unlikely. She had a fever. She went downhill rapidly. The blood culture was negative. It seems unlikely that subacute bacterial endocarditis should be seriously considered. Disposing of the three things in the past history, we have to consider the problem of painless jaundice at the age of sixty-nine. Perhaps the most important of the x-ray findings is the presence of a large spleen. This was questionably palpable, but the x-ray examination confirms that there was a large spleen. Dr. Jones said earlier this morning at Medical Grand Rounds that a large liver and large spleen in the presence of jaundice means that there must be intrinsic liver disease, and not obstructive jaundice. Extrahepatic obstruction should not give this large spleen.

Before dismissing the possibility of biliary obstruction, one would have briefly to consider carcinoma of the head of the pancreas and carcinoma of the bile duct or of the ampulla of Vater with resultant damage to the liver. Against carcinoma of the ampulla of Vater is the absence of a positive guaiac reaction in the stool. The majority of cases should have blood in the stool. Certainly, a common-duct stone can produce jaundice, a large liver and intermittent fever and can go on to a fatal termination without any significant degree of pain, but we have already concluded from the presence of a large spleen that the primary difficulty was within the liver.

What type of liver disease could she have had that would end up with this clinical picture and fatal termination? There was no history that suggests the usual etiologic factor in producing alcoholic cirrhosis. Apparently, the patient had been a neurotic type of person. She may well have had a poor diet, but she certainly was not alcoholic. The possibility of biliary cirrhosis should be considered. The usual term "Hanot's cirrhosis" is confusing. It apparently has been a catch-all for a number of poorly understood conditions. In recent years it has been shown that following virus infections of the liver, chronic hepatitis, progressing to a type of biliary cirrhosis that is consistent with this clinical picture, can develop.

The laboratory findings, as so often happens in the presence of jaundice, are confusing. At least they are to me. She had bile in her stools because

*Assistant in medicine, Massachusetts General Hospital.

they were not clay colored on admission, and there is no mention of clay-colored stools later on. She had normal urobilinogen in the stools and only moderately elevated urobilinogen in the urine. This indicates that there was not a high degree of extrahepatic obstruction. The alkaline phosphatase, being moderately elevated and rising, is suggestive of extrahepatic obstruction. The cephalin-flocculation test was strongly positive, suggesting a considerable degree of liver damage. The cholesterol was very low, as were the cholesterol esters. These indicate severe hepatic damage rather than extrahepatic obstruction.

I am sure the problem on the ward was whether this was extrahepatic or parenchymatous jaundice. Finally, a biopsy was done, which I do not believe can completely answer the question. There was evidence of proliferation of the small bile ducts and an inflammatory reaction, but inspissation of bile in the cholangioles that would ordinarily be seen in extrahepatic obstruction was not present. However, to the pathologist, the findings suggested obstruction in the extrahepatic biliary tract. In spite of that, I believe that the primary difficulty must have been within the liver and that she had some type of cirrhosis, probably biliary cirrhosis.

The other problem is the high, localized elevation of the diaphragm, which raises the question whether this woman had developed a hepatoma. The biopsy did not show it, but it could well have been missed and I think the pathologist is the only one who can answer that.

A Physician: Does the fact that the liver border went down from 11 cm. to 4 cm. mean anything to you?

Dr. Duncombe: I think that it suggests an acute or subacute infection of the liver with cirrhotic changes of the type that has been described following virus infection.

A Physician: Would you comment on the peculiar fever that this woman ran?

Dr. Duncombe: There was some statement here that meant nothing to me. It was noted on one occasion that her general sense of well-being and appetite improved with the high fever. People with severe liver disease and particularly people with cancer in the liver can have a high, irregular, septic temperature, and I assume that it is on the basis of severe liver disease, possibly with a hepatoma.

Dr. Richard J. Clark: Would you consider cholangitis in itself as possibly being the background?

Dr. Duncombe: Whatever the terminal illness causing jaundice of six weeks' duration, some difficulty had been present for some months previous to that period. I do not see how one can rule that in or out completely.

Dr. Tracy B. Mallory: The discharge diagnosis from the wards was subacute atrophy of the liver. I wonder whether there is anyone who wishes to defend that?

Dr. Benjamin Castleman: I believe they made that diagnosis because the liver shrank so rapidly. At least the same examiner thought so.

Clinical Diagnoses

Subacute yellow atrophy of liver.
Arteriosclerotic heart disease.

Dr. Duncombe's Diagnoses

Biliary cirrhosis of liver, probably secondary to virus hepatitis.
Aortic stenosis.
Hypertrophy, left ventricle.

Anatomical Diagnoses

Choledocholithiasis.
Fistula, cystic duct to duodenum.
Obstructive biliary cirrhosis.
Splenomegaly, Banti type.
Cardiac hypertrophy.

Pathological Discussion

Dr. Mallory: At autopsy we found that the liver certainly could not have shrunken much in size because it was still very large, weighing 2520 gm. The apparent shrinkage was due essentially to elevation of the diaphragm.

A large gallstone was found in the common bile duct just above the ampulla, an adequate cause for the development of an obstructive biliary cirrhosis. With further dissection we found that the biliary tree had spontaneously drained itself, that the gall bladder had become a narrow tube with thick fibrous walls but that the cystic duct was dilated to equal diameter and a fistula had developed between the cystic duct and the duodenum. Evidently, drainage had been re-established after a very prolonged period of obstruction of the common duct. At the time of autopsy the inflammatory infiltration in the liver had become more impressive than it was in the biopsy. Either it had extended or perhaps the biopsy was not representative. The surface of the liver was quite finely granular, and the tissue was very firm, and cut with a great deal of difficulty.

The spleen was very large, weighing around 800 gm., and showed on microscopical examination minimal but, I believe, distinct changes suggesting portal hypertension. This is the Banti type of spleen, something that is very rarely seen with a biliary cirrhosis, only with one of very long standing.

The heart was much enlarged, weighing 600 gm., and we could find no reason for it other than an accumulation of a great deal of pericardial fat. There were no valvular lesions, no coronary-artery narrowing, no myocarditis and no evidence that the patient had ever had hypertension. Although heart disease must have been present, I cannot give it a name and say what kind it was.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.
Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. Carroll B. Larson, M.D.
Robert M. Green, M.D. C. Stuart Welch, M.D.
Dwight O'Hara, M.D. Vernon P. Williams, M.D.
Fletcher H. Colby, M.D. Benjamin Castleman, M.D.
Robert L. Goodale, M.D. Hugh R. Leavell, M.D.
Chester M. Jones, M.D. J. Englebert Dunphy, M.D.
Harvey R. Morrison, M.D. Charles H. Burnett, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

HOLIDAY

THE holiday nearest to the hearts of the western world comes opportunely at a time when practically everyone needs a rest after the weeks spent in arduous preparation for Christmas. Unfortunately the long-anticipated day has itself become so exhausting that a second holiday is necessary a week later to recover from the observance of the first — were this provision not rendered ineffective for many by the necessity of dedicating New Year's Day to the task of recovering from the indiscretions of New Year's Eve.

The traditional festival season is long anticipated and unmistakably merry but something of an ordeal.

After all, as some astute philosopher has suggested, it is not so much a rest that man needs in his holidays as it is a change of direction, and this the major festival season of Christianity provides, not only in the intellectual and some of the physical habits of man, but in his point of view as well.

Man is essentially a materialistic being who suspects that in concrete possessions he may find peace and contentment. And still he knows, when he stops to consider it, that nothing is farther from the truth. More radios, more amusements, more automobiles and other faster and more potentially lethal forms of transportation go parallel with more unhappiness, more broken homes, more crime and an increasing loss of true moral values. Those who link their hopes of happiness to ownership are doomed to frustration. Man enters the world naked, it has been said, and naked he leaves it; an observation that has frequently been confirmed in the silent watches by many a family doctor.

With the extremes of poverty and wealth, of discomfort and comfort, of misery and luxury that exist in the world today, greater than ever before, and a general lack of that security that cannot be purchased, it becomes apparent that some other type of currency must be used that is available to all, in the purchase of human peace and understanding.

Coldly scientific or blindly emotional as man may be, still the only currency he can use that cannot be depreciated is one that is measured in spiritual values only.

With which the *Journal* wishes its readers a Merry Christmas, replete with candy canes, and a Happy New Year equipped with flexible but shatterproof resolutions.

MASSACHUSETTS GENERAL HOSPITAL LOOKS AHEAD

THE spirit of research has prevailed at the Massachusetts General Hospital since the founding of the hospital, whose time-honored contributions to medical progress in the nineteenth century are too well known to need reciting. In the first half of the present century also clinical research at the hospital has grown apace. Research laboratories have been set up in every nook and cranny of the Bulfinch Building, and in 1939 a suite of research laboratories was made available for the surgeons with the opening of the White Building.

In 1942 Harvard's Huntington Laboratory moved to the hospital and was given an entire floor in the

old domestic building, where converted kitchens and dining rooms lent themselves well, although far from perfectly, to research purposes. Ultimately most of this building will be devoted to laboratories. The most recent acquisitions of research laboratory space are for the Pediatric and Gynecological services in the Burnham–Vincent Building, which was opened in 1947, and for the Dermatological Service in what was once Ward E and the old Bradlee operating theater.

But even this is not enough. Since the last war funds for research have become available to a

degree undreamed of a decade ago, creating increased opportunities to put investigators to work. These workers on their part have been flocking to the Massachusetts General Hospital in ever-increasing numbers from all parts of the earth.

A building devoted exclusively to research became essential, and at long last there is to be one, with the erection of a six-story structure along the Blossom Street edge of the hospital's property, beginning at the corner of Allen Street, where the Director's house now stands. This house must be abolished, which may cause some regret, but progress demands the sacrifice. There was no other convenient place to put the new building.

Acceding gladly to public need, the hospital will devote major research activities in the new space largely to investigations on cancer, cardiovascular disease and arthritis, with one floor utilized exclusively for the most fundamental type of biochemical research — enzymology — under the direction of the world-famous Dr. Fritz Lipmann.

Although the money is in hand to build the Research Building, that for equipping it remains to be raised. And this will be very costly, because as man gets closer and closer to the facts of life of the cell the more intricate, prodigious and expensive become the implements that he needs to extend the range of his knowledge. No longer can the investigator conduct his studies solely with test tube and old-fashioned microscope. He now needs such items as electron microscopes, ultracentrifuges, electrophoretic apparatus and innumerable radiation detectors. All these and more will constitute the scientific furniture of the Massachusetts General Hospital's new research building. To attempt to set up a research institute without such equipment would be equivalent to sending an army against the enemy equipped only with rifles and hand grenades.

The material of the biologic or medical investigator is living tissue — that of man or of animals, for with no other medium can the way to prevent or cure disease be found. The use of such material, however, imposes great responsibility. In experiments on animals, suffering must be minimized. Studies on man must be planned only with the subject's full understanding and consent, and with every protection against all possible injury.

The top floor of the new research building will be a farm for the animals used in research. An animal lover on the Board of Trustees of the hospital, together with the architect and the staff members, has planned this farm to give its inmates conditions optimal for their welfare.

The participation of human patients in research dates from time immemorial. At the Massachusetts General Hospital it has been greatly facilitated by the installation in 1925 of a special ten-bed research ward. This ward already has had a distinguished career, and it is hoped that one day its history will be written down. Already its contributors have enriched the medical literature. Last March it was finally named the Mallinckrodt Ward 4 in honor of Mr. Edward Mallinckrodt, Jr., one of its principal benefactors. The only fault of the research ward is that it is nowhere near large enough. With the opening of the Research Building certain space now occupied by laboratories will be vacated and can be used to double the size of the Mallinckrodt Ward, which is in close prox-

imity to the site of the new building. This juxtaposition is bound to be fruitful.

Already $1,750,000 has been raised toward the goal of $2,750,000 announced last year — almost enough to construct the building without equipment. The current drive, terminating on January 1, 1950, is confidently expected to bring the fund to practical completion.

ARTHRITIS AND RHEUMATISM FOUNDATION

Chronic arthritis, it is said, has stiffened man's backbone for a period estimated at forty-one thousand nine hundred and forty-nine years. His backbone has now been stiffened, it appears, to the point where he is ready to make some unusual efforts in its behalf.

Little enough has been done for arthritis in these days of multi-million-dollar projects, according to available figures. In spite of the fact that about 7,000,000 Americans suffer from some form of arthritis or rheumatic disease, or about one out of every twenty citizens, only $200,000 a year is being spent on research into the disease and the care of the patients being studied. In contrast to this figure it is interesting to note that $10,587,000 is currently being expended in the field of cancer research, that during the past year $18,665,523 was raised in the annual campaign against tuberculosis and $18,669,299 in that against poliomyelitis, and that $11,000,000 has been appropriated by Congress for the construction of forest trails (but not for the use of arthritic patients).

The Arthritis and Rheumatism Foundation, determined that at last a united effort shall be made to obtain funds with which to fight the Number 1 crippler of mankind, is now engaged in a nation-wide campaign. Started before Thanksgiving it will run until nearly Christmas, with General Lucius D. Clay as chairman. The New England Chapter is doing its share, and is in addition making a survey of the arthritis clinics in the State with the assistance of the Department of Public Health, and the approval of the Council of the Massachusetts Medical Society, which has also established a subcommittee on arthritis of the Committee on Public Health.

NEW ENGLAND COUNCIL

New England medicine had its day — three of them — at the Copley Plaza Hotel in Boston on the occasion of the previously announced eighth annual postgraduate assembly, on November 9, 10 and 11, 1949. The guest speakers on the excellent program were drawn from such diverse points as New York and Baltimore; Chicago; Philadelphia; Durham, North Carolina; Rochester, Minnesota; and Saskatoon, Saskatchewan. The audience, on the other hand, overwhelmingly New Englanders, made up in numbers what they lacked in geographic distribution; 975 physicians registered for the course.

On the premise that postgraduate education is a major factor in medical organization the New England Assembly rates a high mark in the fulfillment of this function.

The status of the Council of the New England State Medical Societies and the relations that exist between it and the New England Postgraduate Assembly are confused in the minds of many physicians in the area. They are, in fact, mutual enterprises serving the same general ends, but independent in organization. The Council promotes improvement in medical practice throughout New England; the Assembly, organized and conducted for reasons of convenience by a committee of the Massachusetts Medical Society, is a mutual undertaking of the six New England state societies and enjoys the blessing of their Council.

The Council, composed of three representatives from each state society, met during the course of the Assembly and heard reports on hospital care for the chronically ill by Dr. W. A. R. Chapin, of Springfield, on the unsuccessful attempts at establishing working relations between the Massachusetts Medical Society and the Massachusetts Hospital Association by Dr. A. E. Parkhurst, and on the conference on public relations held in Chicago in November by Dr. John R. Conlin. A dinner for the entertainment and enlightenment of the New England senators and representatives in Congress was discussed and planned for December 18, prior to their return to Washington.

If any valid criticism of the New England Council of State Medical Societies exists, it is that its

light is still too far under the bushel. Active and interested members of the various New England societies are still unaware of its accomplishments, its aims or even its very existence. There is scarcely a New Englander that is not proud of the traditions, the independent sturdiness and the solidarity of his section of the country. So far as medical standards are concerned, the Council is in a position to aid in preserving all of these, but its activity should be better publicized.

It is announced in the papers that Dr. Richardson, of Boston, expelled a tape worm from a patient which was 100 feet long!

Boston M. & S. J., *December 12, 1849*

MASSACHUSETTS MEDICAL SOCIETY

TWO-WAY MOBILE RADIOS AVAILABLE

The Federal Communications Commission gives preference to physicians for the use of two-way mobile radios.

The installation cost is $17.75 per month. The charge for completed calls in both directions is $0.35; the charge for check-in and check-out is $0.05 and the charge for location reports is $0.05. Physicians within a 30-mile radius of the State House who desire to have one of the 300 available units in their automobiles, should communicate at once with American Communications Co., Inc., 272 Centre Street, Newton (Tel. DEcatur 2-3630).

H. QUIMBY GALLUPE, *Secretary*

NOTES FROM THE MEDICAL EXAMINER

UNEXPECTED DEATH DUE TO INTRACRANIAL TUMORS

The symptoms caused by intracranial tumors extend over months or years in the great majority of cases. For this reason, brain tumors would not be expected to appear in the records of the medical examiner except as incidental findings in patients dying of other causes. A survey of records, however, shows that intracranial tumors are found in a considerable number of cases as the principal cause of death. This note is concerned with some of the mechanisms by which unexpected deaths may be brought about by these lesions.

Gliomas that infiltrate and replace cerebral tissue in "silent" areas of the brain, such as the frontal lobes and portions of the occipital lobes, may attain large size without producing symptoms sufficiently clear-cut to justify careful clinical study. Another such region is the corpus callosum. All too often, the early signs are psychic in nature and are regarded as manifestations of mental instability. The number of unexpected intracranial tumors found at autopsy in mental institutions shows that recognizable manifestations may be wholly of this character throughout the course of a long illness. Meningeal tumors pressing on "silent" areas may enlarge slowly over many years without producing clinical symptoms because compensatory mechanisms allow for the increase in intracranial volume.

The point at which distinctive clinical symptoms are produced is the onset of increased intracranial pressure. This is due either to a sudden increase in intracranial volume, which does not allow time for the compensatory mechanisms to come into play, or to a gradual enlargement, which finally taxes these mechanisms beyond their limits, at which point death may ensue very quickly.

The abrupt and unexpected increase in volume of intracranial contents resulting from a tumor is usually due to a large hemorrhage, especially in a glioblastoma multiforme. The blood vessels in this glioma characteristically show atypical proliferation, which predisposes them to rupture. Glioblastoma multiforme has a tendency to replace considerable amounts of brain tissue, thus delaying the onset of increased intracranial pressure until the tumor is large.

A typical case was that of an eighteen-year-old college student who complained of lack of ability to concentrate, blurred vision and headache of three weeks' duration, thought to have been caused by the strain of examinations. After the examinations, he was admitted to the hospital for study. For fifteen days, he was asymptomatic except for mild headaches. On the sixteenth day, the headaches suddenly became very severe, and a tonic convulsion occurred, followed by shock, respiratory failure and death. At autopsy, a huge glioblastoma multiforme was found in the corpus callosum extending into both occipital lobes. There was massive intraventricular and subarachnoid hemorrhage from blood vessels of the tumor.

Many gliomas become cystic. Although neoplastic cysts usually enlarge slowly, they may expand much more rapidly, causing the symptoms to be sufficiently bizarre to make clinical diagnosis difficult and leading to the suspicion of poisoning or trauma to the head.

In such a case a sixty-five-year-old woman was admitted to the hospital because of stupor for twenty-four hours. The statement of a relative that the patient had for some weeks made repetitious comments and had wandered about the house

in the night was disregarded by her physician. One week before admission, headaches without localization developed, followed by slow speech and increasing drowsiness. Consultants considered encephalitis or some form of poisoning. Death occurred about forty-eight hours after admission to the hospital. There was a cystic glioblastoma multiforme, 4.5 cm. in diameter, in the right frontal lobe. The vague initial symptoms were due to the neoplasm itself, and the terminal episode to the sudden enlargement of the cyst.

It should be emphasized that events such as those in these cases can occur in tumors other than glioblastoma multiforme but are more frequent when that tumor is present. Enlargement of a cystic tumor or progressive growth of a tumor in the region of the aqueduct of Sylvius can lead to relatively sudden death as the result of acute hydrocephalus.

Slowly growing neoplasms occasionally cause unexpected death when they involve areas of the brain from which few or no localizing signs are produced. Atrophy and condensation of the brain compensate for their presence until the size of the tumor precludes further adjustment. Death may then be sudden, usually the result of pontine hemorrhage, as in the case of a sixty-nine-year-old man who died three days after a fall, in which he had injured his neck and lost consciousness. He was thought to have sustained a cerebral laceration or a fracture of the spine. Autopsy showed a very large parasagittal meningioma and pontine hemorrhage. Further study of the history uncovered several episodes suggestive of a minor cerebrovascular accident over the few months preceding death.

Small hemorrhages scattered through the pons often result when the vessels of that region become excessively distorted as a consequence of an expanding lesion within the skull. They are the most frequent cause of death in neglected subdural hematoma and, far more often than is usually supposed, in intracranial tumors, regardless of location.

Intracranial tumors are often discovered in medicolegal autopsies when they are the precipitating cause of accidents, as in the case just described. Falls, automobile accidents and other forms of trauma occur as the result of the unsteadiness and mild mental confusion that often precede definite clinical symptoms of intracranial tumor. The primary purpose of this note, however, is to call attention to mechanisms by which unexpected deaths are *directly* produced by the tumors.

ORVILLE T. BAILEY, M.D.

Assistant Professor of Pathology, Harvard Medical School.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CANCER FACT BOOK

The Department has just prepared a new edition of the *Cancer Fact Book*, which contains a series of charts and tables for the use of physicians desiring data on cancer. Copies of this booklet may be obtained on request.

The booklet contains information regarding the services of the State and State-aided cancer clinics and the Tumor Diagnosis Service, as well as the epidemiology of cancer.

At the present time there are six times as many cancer deaths among males and three times as many among females as there were at the beginning of the century.

Adjustments to take into account changes in the age distribution of the population showed that the rates for females have been declining for the past fifteen years. This downward trend has been more marked for Massachusetts than for the country as a whole.

The sites of cancer showing a downward trend are the mouth, skin, stomach and uterus.

About 30 per cent of all deaths, among women between the ages of forty and sixty, are from cancer.

About 13 per cent of all new cancer cases in Massachusetts are seen in the cancer clinics.

About 85 per cent of all patients seen at the cancer clinics are sent by physicians.

The median age of cancer patients seen at the clinics is several years older at present than in 1930.

There is a four-month delay between first recognizable symptoms and first visit to physician, and a two-month additional delay before the first visit to a clinic.

Of the cases of cancer in which the patients attended the cancer clinics, 36 per cent were classified as probably curable, 31 per cent as possibly curable, and 33 per cent as incurable.

Of patients with skin cases seen within the first month, 80 per cent were alive ten years after treatment. Of those seen later than one month about 44 per cent were alive ten years after treatment.

Of patients with cancers other than of the skin, seen within one month, 39 per cent were alive ten years after treatment, and of those seen after one month, 20 per cent were alive ten years after treatment.

Although pain usually has not been considered a symptom of early cancer, it was present in an eighth of all cancer patients who came to the clinics within two months after the first symptom was noticed.

CORRESPONDENCE

ON THE SOUNDS OF THE HEART

To the Editor: I have admired the painstaking and scholarly quality of Dr. Orias's article on heart sounds in the issue of November 17, of the *Journal*. But is this not an instance of how the attempt to apply graphic instrumental methods has made obscure a matter which is readily clarified by simple observation?

To summarize what I wrote many years ago in the *New England Journal of Medicine*, in an article entitled "The Cause of the First Heart Sound" (**200**:917, 1929), the first heart sound is a tone produced by the sudden assumption of tension by the structures surrounding the ventricular cavities — namely, the ventricular walls and the mitral and tricuspid valves — as the diastolic collapse of the ventricular walls is converted suddenly to a state of tense convexity by systole.

Simple illustrations of comparable tones are as follows. If one pulls sharply on the edge of a handkerchief, previously in loose folds, a tone is produced. If the sail of a boat is suddenly filled by a gust of wind a tone is produced. Or if one blows sharply into a collapsed paper bag a tone is produced. The similar nature of the first heart sound is unmistakable if one observes the exposed heart of a large dog.

If one looks closely at the freely exposed heart of such an anesthetized dog, one sees that there is, in diastole, an instant of flaccid concavity of the anterior surface (the right ventricle) that flaps suddenly into a hard convexity as systole becomes effectual. And if one listens with a small, lightly applied stethoscope the conclusion is inescapable that it is this sudden resumption of convexity and tension that produces the first sound.

Undoubtedly, if one skilled in delicate physiologic technic were to take multiple kymographic tracings of the ventricular surface and of intraventricular pressure, all synchronized with a phonocardiogram, one would obtain objective confirmation of this. But where the mechanism is so clear to anyone who will look, feel and listen understandingly it seems unnecessary to go farther.

FRANCIS W. PALFREY, M.D.

Boston, Massachusetts

TREATMENT OF THROMBOEMBOLIC DISEASE

To the Editor: I was very much interested in the recent article on pulmonary embolism by Roe and Goldthwait in the November 3 issue of the *Journal* and also in the editorial on the same subject appearing in that issue.

I realize full well the importance of statistical analyses, and I also am well acquainted with the fallacy of relying upon them to chart one's course in therapeusis, especially if the statistics do not take into consideration all the pertinent data. It is unfortunate that the authors did not correlate their autopsy statistics with general hospital population according to age and disease and also the magnitude of the operative procedures in the different periods in an effort to determine the true cause of the increased incidence of fatal embolism rather than to blame it on the failure of femoral-vein interruption, as a method of treating thromboembolic disease.

Realizing what an important step in the treatment of thromboembolic disease that interruption of femoral veins has been since Homans first described it in 1934 and for fear that this article will be quoted (as it already has to me as damning evidence that the procedure is of little value in the therapy of this disease), I feel it my duty to point out that the increased number of cases of fatal embolism at the autopsy table in the past five-year period, 1943–1947, certainly is not because this method has failed in the majority of patients that have been so treated. In fact, the inference that should be drawn from the statistics quoted in the article is that more patients should have had their femoral veins interrupted, since in this five-year period interruption was performed in only 10 of the 92 fatal pulmonary emboli. It should also be pointed out that this method of treating thromboembolic disease was not generally accepted throughout the Massachusetts General Hospital. In fact, it was only on the East Surgical Service while Dr. Arthur W. Allen was chief and on his patients and mine and a few others on the private side that a policy was carried out in which femoral-vein interruption was the method of choice in the treatment of thromboembolic disease in all its various manifestations.

There is no question that this article is an important one, since it draws to the reader's attention that we have not solved the problem of thromboembolic disease. The subject certainly needs further investigation, but until we have better methods at our disposal to prevent massive pulmonary embolism the operation of femoral-vein interruption in the hands of a *competent surgeon* should not be discarded. Those that recommend it fully realize that it is not a perfect procedure, but let us not incriminate it too severely from this report, when in 92 cases of fatal pulmonary embolism it was not used in 82, or 89 per cent.

ROBERT R. LINTON, M.D.

Brookline, Massachusetts

BOOK REVIEWS

Diabetes and its Treatment. By Joseph H. Barach, M.D. 8°, cloth, 326 pp., with 73 illustrations, 50 tables, and 2 plates. New York: Oxford University Press, 1949. $10.00.

This book is written by an author who knows diabetes well and deserves the approbation of every physician in the United States for his courage in exposing diabetic quackery wherever found. Unfortunately, the book is expensive, because it contains 326 numbered pages and approximately 200 unnumbered pages devoted to a system of diets for men, women and children, all of which are duplicated in his other book, entitled *Food and Facts For the Diabetic*, which was written for patients. There are 73 figures and 60 tables.

Commendable initiative throughout is shown by the writer. He draws upon his own practice to illustrate the advantages of this or that kind of treatment. The volume is decidedly *sui generis*, although the literature is also very well covered. The text is expressed forcibly, and nearly every page is thought provoking; for example: "Obviously the diabetes that appears at the age of 10 will have many more years to produce changes in the tissues and organs of the body than the diabetes that comes at 60; so that the later in life that diabetes appears, the less chance it has to shorten life." One wonders whether the diabetes that is diagnosed at the age of sixty has not been latent in many cases for a decade or more and, therefore, whether the foregoing really states the situation fairly. Best and Kendall Emerson, Jr., have both intimated the presence of a prediagnostic diabetic era and the need for the vigorous and active treatment of such cases. At present this can be done only by the prophylaxis of obesity. The following statement about obesity is worth wide dissemination. "Since there is no known advantage in being overweight, we may very well offer the blanket advice to everyone to avoid obesity." Dr. Barach is equally incisive about the marriage of a diabetic person: "My advice to a young member of my own family would be not to marry a diabetic, and my advice to a diabetic would be not to marry at all, unless other conditions in his or her life are favorable." In dealing with heredity, however, the author inadvertently has given a wrong impression in stating that all the children of two diabetic parents will develop diabetes. Theoretically, they will develop diabetes, but practically they will not do so unless they live long enough to reach the age at which diabetes is likely to break out. The chances have been computed that before those ages are reached at least half the offspring will die of other diseases.

Throughout the volume one finds words of wisdom and new viewpoints when old problems are presented. There is an instructive table of the common complaints of the patient and a novel discussion of weights and diets. Deformities are recognized as occurring quite often in the children of diabetic parents, and the author also calls attention to the frequency with which lesions of the feet of older patients are connected with and often dependent upon congenital deformities of the feet themselves. It is unfortunate that when the 47 per cent mortality and even 45 per cent mortality for thigh operations upon diabetic patients in certain localities are referred to, attention is not called to the low mortality of McKittrick and his group — 5.5 per cent, according to a recent paper in the *Annals of Surgery* (**130**: 826, 1949) — and to their conclusions that transmetatarsal operations make many thigh operations unnecessary. Reference is made to the routine practice of giving glucose to the children just born of diabetic mothers, but attention is not called to the hypoglycemia, which is often found in the off-

spring of nondiabetic parents, or to the therapeutic omission of the use of glucose in perhaps the largest series of infants born of diabetic mothers reported from one clinic.

A doctor or student who wishes to investigate a problem in diabetes will find the book full of suggestions.

The book is heartily recommended — minus the diet tables, which could be summarized and thus reduce the cost and make it available to more readers. Moreover, the diet of any diabetic patient varies from day to day according to exercise and mode of life, and he must be taught how to make adjustments.

Practical Aspects of Thyroid Disease. By George Crile, Jr., M.D. 12°, cloth, 355 pp., with 101 illustrations. Philadelphia: W. B. Saunders Company, 1949. $6.00.

This monograph of 355 pages presents in a large measure the personal experience of the author in diagnosis and treatment of diseases of the thyroid gland. In an effort to make the volume succinct and perhaps more practical, the author purposely avoids presenting a study of the much larger accumulated material of thyroid pathology from the Cleveland Clinic gathered under George Crile, Sr., and his associates. In only a few less common pathologic conditions of the thyroid gland does he employ this fuller material in his discussion; this too, however, is interpreted very much in the light of his own personal experience.

The book opens with a brief discussion of the physiology and pathology of the thyroid gland and presents well established concepts generally accepted in the prevention and treatment of endemic goiter. The material is divided into chapters dealing with the diagnosis and the treatment of hyperthyroidism in its various aspects and dealing also with the various complications of treatment of thyroid disease. Antithyroid therapy both as primary medical treatment and as a preparation for surgery is discussed, and a very brief discourse is given on radioactive iodine. The reviewer does not entirely agree with the author that radioactive iodine is "safe, effective and simple," and believes such conclusions are not yet warranted in the light of insufficient experience to substantiate such a statement. The author does, however, advise caution in the employment of this drug but concludes that radioactive iodine bids fair to become the preferred treatment for all patients with Graves's disease. This the reviewer very much doubts and would caution that this material be used only in the hands of those thoroughly trained in the use of irradiated isotopes.

The description of the technic of thyroidectomy is outlined as practiced by the author. In all probability this is not the technic that has been employed in the past in the Cleveland Clinic. The surgical technic as described, however, is sound and practical and, in general, similar to that advocated in other large thyroid clinics in the country. One is glad to note that exposure of the recurrent laryngeal nerves is advocated. The volume proceeds, then, with a discussion of the various pathologic conditions of the thyroid gland such as thyroiditis and carcinoma. A brief chapter is given, also, on the types of anesthesia. It is interesting to note that the old arguments for the use of local anesthesia are still in force, and the dictum is advanced that a more adequate respiratory exchange can be obtained with greater ease under local anesthesia than in patients who are relaxed under general anesthesia. Certainly, this would not be agreed to by everyone; respiratory exchange can be obtained in all types of thyroid conditions under general anesthesia if an endotracheal catheter is used. In the hands of expert anesthesiologists, intratracheal anesthesia can be employed without trauma and without any increased morbidity and certainly adds to the patient's comfort and greatly reduces the possibility of obstruction.

The chapter on carcinoma of the thyroid gland reflects almost entirely the views of the Cleveland Clinic and in a large measure represents the work of Dr. Allen Graham. The descriptions of the various types of carcinoma arising in the gland are in large measure similar to other classifications but perhaps are not quite so practical as the classification given by Warren and Meissner. One also is at a loss to understand whether the author advocates the removal of discrete adenomas, which in so many clinics are thought to be very definite precursors of carcinoma of the thyroid gland, or whether he prefers to wait until the clinical diagnosis of carcinoma is made before discrete adenomas are removed. This discussion does not present a completely convincing argument for or against such now quite universally accepted prophylaxis.

The material is well presented, well organized and extremely well illustrated. It should prove valuable to the general practitioner who does not have a large experience in the treatment of thyroid disease, but it would not be of great help to the internist or surgeon who has had a reasonably large experience in the recognition and treatment of various pathologic conditions of the thyroid gland.

A moderate number of cross references is given. To the critical reader, if he desires, they present sufficient material to clear up certain controversial points that are not entirely clarified in this volume.

The book is well printed and it is to be recommended to the type of reader mentioned above.

Food and Facts for the Diabetic. By Joseph H. Barach. 8°, cloth, 113 pp., with 16 illustrations and 21 tables. New York: Oxford University Press, 1949. $4.00.

This volume consists of 113 pages of text, including tables and index, but also 198 unnumbered pages on which are 252 diets for men and women of the ages of twenty-five and above, as well as diets for children and emergencies. The diets are calculated on the basis of body build — small, medium and large — for 25.0, 27.5 and 30.0 calories per kilogram of body weight respectively. One could hardly blame the patient if he asked why he should purchase so many diets that are not designed for him.

The text is admirable, and one would hope that all diabetic patients would become familiar with it, although the style is rather more for nurses and dietitians and the more intelligent diabetic patients than for the rank and file. The advice given the patients is stated so clearly and is so sound that it would be meticulous and, indeed, unfair to point out the few sentences or even paragraphs, which undoubtedly will be altered in a subsequent edition.

NOTICES

MISSISSIPPI VALLEY MEDICAL SOCIETY

The fifteenth annual meeting of the Mississippi Valley Medical Society will be held at Springfield, Illinois, on September 27, 28 and 29, 1950, under the presidency of Dr. N. G. Alcock, of the University of Iowa.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1950 ESSAY CONTEST

The Tenth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1950. The Society will offer a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fifteenth Annual Meeting of the Mississippi Valley Medical Society to be held in Springfield, Illinois, September 27, 28 and 29, 1950, the Society reserving the exclusive right to first publish the essay in its official publication — the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1950. The winning essays in the 1949 contest will appear in the January, 1950, issue of the *Mississippi Valley Medical Journal.*

Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

POSITION FOR QUALIFIED BACTERIOLOGIST IN VETERANS ADMINISTRATION

A vacancy exists for a qualified bacteriologist in the pathology laboratory of the Veterans Administration Center, Los Angeles 25, California. The laboratory is located in the

General Medical and Surgical Hospital of the Center. The position pays $6400 a year, and the Civil Service classification is known as GS–12.

Applicants must have successfully completed a full four-year course leading to a degree with major study in the biologic sciences in a college or university of recognized standing, with courses totaling at least twenty semester hours in general and medical bacteriology, or any combination of bacteriology and biology including at least ten semester hours in general and medical bacteriology. Applicants must show four years' experience, at least two years of which includes experience in medical bacteriology in a research or clinical laboratory. The other years may include experience in teaching medical bacteriology in a medical school of recognized standing. A doctor's degree in bacteriology or serology may be substituted for the latter experience.

Interested applicants are urged to send Standard Form 57 (blanks can be obtained at any post office) to the Personnel Officer, Veterans Administration Center, Los Angeles 25, California.

FUNDS FOR RESEARCH IN CARDIOVASCULAR DISEASE

A portion of the funds collected during the 1949 Heart Campaign has been set aside for research in cardiovascular diseases, according to C. Sidney Burwell, M.D., chairman of the Research Allocations Committee of the Greater Boston Chapter of the Massachusetts Heart Association.

Applications from institutions in Greater Boston are invited. Inquiries should be addressed to Dr. Burwell at the Peter Bent Brigham Hospital, Boston.

DAMON RUNYON CLINICAL RESEARCH FELLOWSHIPS

The American Cancer Society announces the availability of Damon Runyon Clinical Research Fellowships. These fellowships, inaugurated last year, are made possible by a grant from the Damon Runyon Memorial Fund for Cancer Research to the American Cancer Society. They are administered by the Society upon recommendation of the Committee on Growth of the National Research Council. In most cases a fellowship will provide a period of training in a hospital under the guidance of a qualified clinical investigator. However, fellowships may be awarded for training in a basic science provided that such training is directed toward preparing the fellow for clinical cancer research. They are limited to men and women holding the M.D. degree. It is emphasized that they are intended to promote training in clinical cancer research rather than in cancer diagnosis and therapy.

Applications submitted prior to March 1, 1950, will be acted upon during April. Fellowships approved at that time may become effective July 1, 1950, or at such other time as will meet the convenience of the fellow and the institution. Communications should be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

DECEMBER 17. Guest Speakers' Conference. Bone Marrow Aspiration in Diagnosis of Disorders of the Blood. Dr. Simon Propp. Staff Conference Room, The Springfield Hospital, Springfield. 11:00 a.m.

DECEMBER 19. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

DECEMBER 20. South End Medical Club. Page 888, issue of December 1.

DECEMBER 20. Boston City Hospital House Officers' Association. Page 950, issue of December 8.

DECEMBER 21. Association of School Physicians of Massachusetts. Page 950, issue of December 8.

DECEMBER 28 AND 29. American Association for the Advancement of Science. Page 350, issue of September 1.

JANUARY 9. New England Cardiovascular Society. Page 724, issue of November 3.

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

JANUARY 12. Common Skin Diseases. Dr. John L. Fromer. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 18–20. Conference on Cardiovascular Diseases. Page xvii, issue of November 10.

FEBRUARY 20. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

FEBRUARY 20–23. American Academy of General Practice. Page 252, issue of August 11.

APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.

MAY 3. Norfolk District Medical Society Anniversary Dinner.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991.

DISTRICT MEDICAL SOCIETY

NORFOLK

JANUARY 24.
FEBRUARY 28.
MARCH 28.
MAY 3. Anniversary Dinner.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 22

FRIDAY, DECEMBER 23

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

TUESDAY, DECEMBER 27

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, DECEMBER 28

*12:00 m. Clinical Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*Open to the medical profession.

Dr. Wise, as a holiday measure
That his neighbors and relatives treasure,
Puts his* Journal *away
For some part of the day
And devotes himself wholly to pleasure.

6